FDA ODAC Briefing Document for NDA 21-236

IntraDose® (cisplatin/epinephrine) Injectable Gel

for

Recurrent Squamous Cell Carcinoma

of the

Head and Neck

From Division of Oncology Drug Products
Center for Drug Evaluation and Research
United States Food and Drug Administration

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edited by Grant Williams, MD

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CLINICAL REVIEW OF NDA 21-236

I. Introduction and Background

A. Abstract of the Proposed Label

1. **Drug Established and Proposed Trade Name** : IntraDose®
2. **Drug Class:** Antineoplastic
3. **Sponsor's Proposed Indication:** "Recurrent squamous cell carcinoma of the head and neck in patients who are not considered curable with surgery or radiotherapy"
4. **Dose:** 0.25 – 0.5 mL/cm3 of tumor volume to a maximum of 10 mL
5. **Regimen:** Weekly administration for 6 weeks with re-measurement and recalculation of the dose at each visit.
6. **Age Groups:** not specified

B. State of Armamentarium for Indication(s)

At this time there are several management options available for patients within the targeted population. There are, however, no agents approved specifically for this indication "Recurrent squamous cell carcinoma of the head and neck." Much of the available therapy includes two- and three-drug combinations of FDA-approved drugs such as cisplatin, 5-FU, methotrexate, paclitaxel and docetaxel. Additional details may be found later in this review.

Biological therapies have been investigated although there are no currently available agents approved for this indication. Pivotal trials of potential biological approaches are underway in the same or similar indications.

Nd:YAG and CO2 laser therapy is also used in this setting.

Surgery in this sometimes a palliative option in this setting. Similarly, IntraDose® is best viewed as a palliative option.

C. Important Milestones in Product Development

1. **19 December 1994 Meeting:** several key issues were addressed including treatment goal endpoints, general design of the two studies, importance of capturing local toxicities, control arm, blinding and statistical concerns were discussed.

2. **3 December 1997 Meeting:** Issues clarified include photographs (all will be submitted), the primary endpoint and analyses, the primary analysis will be symptom improvement with tumor responses playing a supportive role, "Symptomatic Response" strongly recommended as the primary efficacy endpoint and the association of meeting the treatment goal and the MTT responding will be analyzed.

3. **28 October 1999 Meeting:** Clinical benefit and response analyses should be based on the intent to treat (ITT) population with all other analyses playing a supportive role, subset analysis for patients who are considered incurable with surgery should be done, and prior therapies must be extensively described to document refractoriness of disease.

4. **8 May 2000 Response:** several statistical issues were clarified. Further details may be found later in this review.

   Additional information about the specific issues may be found in the Regulatory History summary of this product contained within this NDA review.

- Written documentation of FDA agreements/expectations/concerns

  See Appendix D for a discussion of the regulatory history of IND 38,356/NDA 21-236. Further details may still be found in the actual minutes derived from meetings and in written FDA responses.

- Pertinent FDA guidance documents

  ICH E3 – Structure and Content of Clinical Study Reports
  ICH E6 – Good Clinical Practice: Consolidated Guidance
  ICH E8 – Guidance on General Considerations for Clinical Trials
  ICH E9 – Statistical Principles for Clinical Trials
  ICH E10 – Choice of Control Groups in Clinical Trials
  Guidance for Industry: Fast Track Drug Development Programs – Designation, Development and Application Review

- Pertinent advisory committee meetings

  There have been no recent Oncology Drug Advisory Committee meetings relevant to this NDA within the last 5 years.

- Prior FDA reviews

  NDA 21-161 (Foscan®) for a similar indication was determined to

be not approvable based on study design, risk/benefit concerns, and other issues. Foscan® was recently approved in Europe in June, 2001 after an initial unsuccessful attempt in 2000.

- Major issues that arose during clinical trials, for example, study design, safety, or ethical considerations. How were they resolved?

  During the early phase of the study, there were a series of six cerebrovascular events (stoke, CVA) observed in the initially enrolled patients. This prompted the applicant to suspend accrual, convene a meeting of their investigators and advisors, and search for common precipitating factors. The conclusion was that these strokes were possibly precipitated by acute spasm of the carotid artery in the presence of high local concentrations of epinephrine which, if there were critical stenosis or an ulcerated atherosclerotic plaque present in the same local vicinity, hemorrhagic or ischemic cerebral infarct could occur. Measures employed to minimize this possibility included avoidance of any tumor for injection that was abutting or in close proximity to the carotid artery.

  Issues regarding the endpoints and analyses for the two studies arose during accrual. The essence of prior advice from the Division was conveyed on such items as the treatment goals, clinical responses, local toxicity, correlation between clinical benefit and tumor responses and the primacy of clinical benefit as the most important efficacy endpoint. Meetings and written responses provide further details about the Division's advice (Appendix D).

D. Other Relevant Information

IntraDose® has not been approved for marketing in other countries.

E. Important Issues with Pharmacologically Related Agents

The active antineoplastic moiety in IntraDose® is **cisplatin**, an FDA-approved anticancer agent that induces cytotoxicity by binding to and cross-linking DNA. Cisplatin and its analog carboplatin are active, although toxic, drugs. Neural, renal and hematopoietic tissues are most susceptible. Clinical toxicity is manifested as distal paresthesias, ototoxicity, myelosuppression and nephrotoxicity.

Bovine **collagen** is also a component of this product whose purpose is to retain the cisplatin in the local area and thus provide an increased local therapeutic index. Concerns over the inclusion of animal-derived material revolve around transmissable adventitial agents such as the prion causing bovine spongiform encephalitis. The sponsor has procedures in place to ensure production batches are free of such agents.

Epinephrine is a third component of IntraDose® whose purpose is to limit local tissue blood flow thereby increasing the local therapeutic index.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

- The chemistry reviewers are currently considering the stability of the reconstituted product at room temperature.

- The reconstitution procedure is more involved than standard reconstitution and dilution procedures generally familiar to medical oncologists and oncology pharmacists. The chemistry reviewers have raised questions about the homogeneity of the injected product when the labeled procedure is followed.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Study 516-99-PK was a study performed in 16 patients. IntraDose® was injected intratumorally according to the proposed labeling at the recommended dose of 0.5 mL per cubic centimeter of tumor volume. Systemic exposure was determined by plasma sampling and AUC determination. The summarized results indicate that considerable variability in all pharmacokinetic parameters was observed and could not be explained by differences in age, gender or dose administered. Moreover, the median t_{max} for total platinum after intratumoral administration of IntraDose® [1.5, range 0.08 – 24 hours] was comparable to the median t_{max} [1.2, range 1.0 – 1.4 hours] following conventional intravenous administration of cisplatin. These findings suggest that the applicant's goal of providing prolonged local exposure of tumor to high levels of platinum may not be realized.

C. Pharmacodynamics

There were no specific pharmacodynamic data collected or studies performed in the two pivotal trials. The pharmacokinetic study, 516-99-PK, was submitted in support of this NDA.

IV. Description of Clinical Data and Sources

A. Overall Data

The data submitted from which the two studies have been reviewed include electronic databases 'Study 414' and 'Study 514' in MS ACCESS which were converted from SAS Transport Files. Several tables within these databases used in the review are identified in the table below. Case report forms (CRF's) were submitted in .pdf format. 'Review cards', which were poster-size pages

containing the most relevant clinical data in one place, were also submitted. In addition, serial digitized photographs of most subjects were also submitted.

Table	Study Information
'ame'	Adverse medical events/intercurrent illness log
'conmed'	Concomitant therapy log
'conthrp'	Concomitant therapy log for any primary or metastatic malig.
'demog'	Patient demographics
'disehist'	Screening disease history
'dosing'	First treatment dosing record
'goalinv'	Investigator assessment treatment goal questionnaire
'goalpt'	Patient assessment treatment goal questionnaire
'inex'	Screening patient eligibility checklist
'krnfsky'	Karnofsky performance status
'qol'	FACT-H&N (version 3)
'rndm'	Randomization of each patient
'serum'	Local laboratory serum chemistry data
'tumoreval'	Local tissue conditions
'tumorscr'	Disease status
'vital'	Vital signs monitoring

B. Table Listing of Clinical Trials

Study Number	Clinical Phase	No. Patients	Study Location	Study Dates	Tumor Type	Study Type
414-94-2	III	110	US, Canada Multi-center	6/95 – 3/00	HNSCC	Pivotal
514-94-2	III	115	Multi-center Europe/Israel	6/95 – 3/00	HNSCC	Pivotal
516-99-PK	I	16	US, Europe		HNSCC	Supportive
39-92-P	I	45	US		Breast (13) HNSCC (14) Melanoma (3) Other (14)	Supportive
403-93-2	II	67	US		Breast (13) Esophageal (8) Melanoma (13) Other (30)	Supportive
503-93-2	II	59	Europe S. Africa		Breast (13) Esophageal(16) Melanoma (15) Other (15)	Supportive

C. Postmarketing Experience

No postmarketing information exists for IntraDose®.

D. Literature Review

A series of tables summarizing the literature describing the active combination drug may be found in Appendix F.

A review of the relevant literature suggests chemotherapy is active in this disease as single agents, doublets and triplets leading to response rates in the 14 – 58% range with durations of response – when reported – in the 1.5 to 6.8 month range.

V. Clinical Review Methods

A. Describe How the Review was Conducted

The two pivotal trials were reviewed separately although the approach taken was identical because of their similarity in design. The team clinical pharmacologist reviewed Study 516-99-PK. The additional supportive studies were not reviewed.

The clinical and statistical reviewers evaluated and sought to verify the sponsor's tumor response and clinical benefit claims using the electronic databases and CRF's. Specific efforts were directed at reviewing the primary tumor dimension data and drug administration data. These efforts identified several issues of concern surrounding data integrity, compliance with the protocol and study conduct. Independent calculations of the tumor volumes, drug administration volumes and durations of responses were compared with the applicant's findings. Whether the calculations confirmed or failed to verify the applicant's was noted in tabular format at the appropriate location in this review.

B. Overview of Materials Consulted in Review

The applicant's IND, #38,356, was originally opened in 1991 and was consulted frequently during the NDA review for specific language regarding AE's and agreements between the applicant and the Agency.

Descriptions of the sources of data for this review were provided earlier in this Review and include electronic database information, case report forms, 'treatment cards' and digitized photographs.

References to relevant literature are documented in tables summarizing the studies' key findings. The citations are appended to this review.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

Concern over the site at UCLA under the direction of Dr. Dan Castro arose during the review and this site has been specifically selected for careful review. The

review team has been apprised preliminarily of DSI's findings by Dr U's and it is his opinion that the patient data can be used in the review of this NDA.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards?

The applicant states that the investigators were responsible for ensuring that the studies were conducted according to Good Clinical Practices found in 21 CFR 50, 56 and 312. The applicant also states that site monitoring was conducted in accordance with Guidelines for the Monitoring of Clinical Investigations, January 1988, and also under SOP's of Matrix. All regulatory, institutional, privacy and IRB obligations were the responsibility of the investigators (v. 21, p. 44). In addition, all clinical trials were conducted according to the ethical principles of the Declaration of Helsinki (v. 21, p. 34).

E. Evaluation of Financial Disclosure

The applicant addressed financial disclosure by providing a list of all investigators and sub-investigators and indicating whether or not financial disclosure information was returned to the company. For each of the two studies comprising this NDA, there appear to be approximately one-half of the investigators having complied with the sponsoring company's request for information. One unrestricted grant of approximately $60,000 to Dr. Costantino was noted. This site was also selected by the review team based on protocol violations.

VI. Efficacy Review

A. Integrated Review of Efficacy (Not included in this document; see the Overall Summary in section IX of this review and also refer to FDA efficacy review sections of individual studies)

B. Detailed Review of Trials by Indication

1. Study 414-92-2

A Randomized Double-Blind, Placebo Controlled Study to Evaluate the Effect of Cisplatin/Epinephrine Injectable Gel (Product MPI 5010) When Administered Intratumorally for Achievement of Treatment Goals in Recurrent or Refractory Squamous Cell Carcinoma of the Head and Neck

1.1 Location of information reviewed in NDA:

Study Item	Volume
Study Report	4.15
Protocol	4.21
CRF's	electronically submitted in .pdf
Database documentation	Access database '414'
Integrated Summary of Efficacy	4.164, pp. 111-225

1.2 Important Study Dates

Study Period	15 Jun 95 – 22 Mar 00
First Patient's First Treatment	15 Jun 95
Last Patient's First Treatment	06 Jan 00

1.3 Review of the protocol and amendments

Please see the review of the protocol and amendments appended to the end of this review template.

1.4 Analysis of Study 414

1.4.1 Details of Trial Conduct and Analysis

This was a randomized, blinded 44-center US - Canadian study with 110 patients enrolled. Per protocol, only the 86 patients from stratum 1 and 2 with an MTT (most troublesome tumor) 20 cm^3 were intended for the efficacy analysis. The data submitted to the FDA are derived from patients who were enrolled between 15 June 1995 and 22 March 2000. (v. 13, p. 23).

The sponsor states that the investigators were responsible for ensuring that the study was conducted according to Good Clinical Practices found in 21 CFR 50, 56 and 312, also in accordance with Guidelines for the Monitoring of Clinical Investigations, January 1988, and also under SOP's of the sponsoring company. All regulatory, institutional, privacy and IRB

obligations were the responsibility of the investigators (v. 21, p. 44). In addition, all clinical trials were conducted according to the ethical principles of the Declaration of Helsinki (v. 21, p. 34).

The sponsor also describes in summary form many deviations from the protocol (v. 14, p. 385-396).

1.1.2 Baseline Patient Characteristics

One hundred ten patients with a MTT were enrolled, of which 109 received treatment. Breakdown by **gender** shows that 24 (21.8%) were women and 86 (78.2%) were men.

All Strata	Active CEG	Placebo Gel	Total by Gender
Men	60	26	86
Women	17	7	24
Total by arm	77	33	110

The same table (excluding stratum 3, i.e. patients with volume > 20 cm^3) shows the breakdown by gender in the population which form the basis for efficacy claims.

Strata 1 & 2	Active CEG	Placebo Gel	Total by Gender
Men	50	17	67
Women	12	7	19
Total by arm	62	24	86

Reviewer comment: These numbers agree with the sponsor's analysis. (Table 11-1, v. 15, p. 95)

Ethnic representation, described in the electronic database (Access table 'demog') included 85 (77.3%) patients identified as "White", 10 (9.1%) as "Hispanic", 8 (7.3%) as "Black", 4 (3.6%) as "Asian" and 3 (2.7%) as "American Indian".

Ethnic Identification	Active CEG n = 62		Placebo Gel n = 25	
White	51	82.3%	76.0%	19
Black	4	6.4%	4.0%	1
Hispanic	6	9.7%	4.0%	1
American Indian	1	1.6%	8.0%	2
Asian	0	0.0%	8.0%	2

Reviewer comment: The values essentially agree with sponsor's reported results (Table 11-2, v. 15, p. 95).

The **age at enrollment** ranged from approximately 34 to approximately 92 years with a median of approximately 63 years. (ACCESS table 'demog')

Age	Active CEG		Placebo Gel	
	Stratum 1 n=31	Stratum 2 n=31	Stratum 1 n=12	Stratum 2 n=13
Range	33.7 - 84.7	42.8 – 87.8	48.8 – 82.7	40.1 – 85.8
Median	62.7	65.4	61.6	61.5

The values essentially agree with sponsor's reported results (Table 11-1 and 11-2, v. 15, p. 95).

The **Karnofsky Performance Status** at enrollment ranged from 50 to 100 with a median of approximately 80 years. (ACCESS table 'krnfsky'). The following table shows the distribution between arms and strata.

KPS	Active CEG		Placebo Gel	
	Stratum 1 n=31	Stratum 2 n=31	Stratum 1 n=12	Stratum 2 n=13
Range	50 – 100	50 – 100	60 – 100	40 – 100
Median	80	80	85	80
Mean	78	79	83	79

The values essentially agree with sponsor's reported results (Table 11-3, v. 15, p. 97).

Histopathological grade was derived from the submitted electronic database (Access table 'tumorscr'). The key to the numerical representation of the histopathological grade is shown below the table. Although 62 patients on the active arm and 25 on the placebo arm were randomized, there were only 25 and 17 descriptions histological grade that were included in the table 'tumorscr' on each arm respectively.

Histopathology	Active CEG		Placebo Gel	
	Stratum 1 N=25	Stratum 2 n=17	Stratum 1 n=9	Stratum 2 n=9
Range	1.0 – 3.0	1.0 - 3.0	1.0 – 3.0	1.0 – 3.0
Median	2.0	2.0	2.0	2.0
Mean	2.3	1.9	2.1	2.0

Key to Histopathology Scores:

Well differentiated	1.0
Moderate to well differentiated	1.5
Moderately differentiated	2.0
Moderate to poorly differentiated	2.5
Poorly differentiated	3.0

Reviewer comment: There does not appear to be appreciable differences in histopathological grade between the arms or strata.

The applicant did not perform this analysis.

1.1.2.1 Prior Therapy

Prior therapy for head and neck cancer in this study included surgery, radiotherapy, chemotherapy and possibly other local therapy such as Nd:YAG or CO2 laser treatments for local ablation.

Prior Therapy	Active CEG					
	Stratum 1 n=31			Stratum 2 n=31		
MODALITY	S	R	C	S	R	C
Surgery (S)	1	14	0	1	11	1
Radiotherapy (R)	--	1	0	--	0	1
Chemotherapy (C)	--	--	0	--	--	0
All 3 Modalities	15			17		

Prior Therapy	Placebo Gel					
	Stratum 1 n=12			Stratum 2 n=13		
MODALITY	S	R	C	S	R	C
Surgery (S)	1	7	0	0	5	0
Radiotherapy (R)	--	1	1	--	2	0
Chemotherapy (C)	--	--	0	--	--	0
All 3 Modalities	2			6		

Reviewer comment: By inspection, the arms appear to be balanced with regard to prior therapy.

1.1.3 Therapy Delivered

The ITT population of all 110 patients in this study is used in the FDA analysis of therapy delivered. Review of the claimed responders and clinical benefitters suggests that compliance after the first few visits drops significantly. The following table describes the drop-off as a function of visit number:

No. of Treatments Received	Active CEG n = 62	Placebo Gel n = 24
1	62 (100.0%)	24 (100.0%)
2	56 (90.3%)	23 (95.8%)
3	42 (67.7%)	17 (70.8%)
4	28 (45.2%)	6 (25.0%)
5	15 (24.2%)	1 (4.2%)
6	10 (16.1%)	0 (0.0%)

1.1.3.1 Termination

Review of the table 'studycomp' suggests the two predominant reasons for patient termination from the study were systemic disease progression and target tumor progression. The following table below indicates the relative frequencies of the various reasons for termination:

Reason for Termination	Number (%)
Systemic disease progression	28 (25.6)
Progressive disease of the target tumor	22 (20.0)
Patient request, not otherwise specified	18 (16.3)
Unacceptable adverse events/local toxicity	15 (13.6)
Death on study	12 (10.9)
Need for other therapy not per protocol	5 (4.5)
Completed study	1 (0.9)
Other:	9 (8.2)
Admitted to hospice	1
Return home out of state	1
"Treatment Failure"	1
"Company request"	1
Lost to follow-up	1
Non-compliance	1
MTT too close to vital structure	2
"Adequate response"	1
Total	110 (100.0 %)

Reviewer comment: The principal results agree closely with the applicant's analysis. The Study Report (v. 15, p. 88) states that 44% of patients discontinuing study participation for local or systemic disease progression. Slight differences may be noted in the other reasons for study terminations from Tables 10-3 and 10-2 (v. 15, p.90-91) when compared to this table, but they are not of significant magnitude to affect the overall results of this study.

1.1.4 Evaluation of Efficacy

1.1.4.1 Sponsor's Evaluation of the Primary Efficacy Endpoint

The applicant claims an objective MTT response (CR or PR) in the blinded phase of 34% (21/62) of patients randomized to strata 1 and 2 of active CEG (Table 11-9, v. 15, p. 102).

The applicant also claims a clinical benefit in 34% (21/62) of patients randomized to the active CEG arm (strata 1 and 2 only) (Table 11-19, v. 15, p. 112).

The applicant has examined the association between MTT response and clinical benefit and finds that 48% (10/21) of patients who achieved an MTT response (during the blinded phase) also achieved a clinical benefit.

Using the applicant's claimed rate of blinded phase MTT response and rate of clinical benefit, the following table may be constructed:

Study 414		MTT Blinded Phase Objective Response with Active CEG?		Total with Active CEG
		Yes	No	
Clinical Benefit with Active CEG?	Yes	10	11	21
	No	11	30	41
Total with Active CEG		21	41	62

Reviewer comment: The table above suggests that the correlation between a blinded phase MTT objective response and clinical benefit is low. Statistical analysis reveals $\chi^2 = 2.68$ (df=1, p=0.10) which suggests non-significance.

1.1.4.2 Medical Officer's Evaluation of the Primary Efficacy Endpoints

The regulatory history of this NDA and the reviewer's summary of the study protocol (with a summary of each amendment) may be found in Appendices A and D. Section 9.5.5 of the study protocol states, "Primary efficacy analysis of tumor response of the MTT will be performed excluding the third stratum" (that is in patients with tumors less than 20 cm^3.

A review of past discussions between the applicant and the division reveals that clinical benefit in the form of "symptom improvement" was to be the primary efficacy endpoint and that tumor responses were to be supportive (meeting minutes 12/3/97). Indeed, a strong correlation between patient benefit and tumor shrinkage was to be required (response to applicant 5/8/00).

The following is the medical reviewer evaluation of response and clinical benefit. Efficacy data from of the each of the objective or clinical benefit responses claimed by the applicant were carefully reviewed to evaluate adherence to the protocol and data quality. A summary of the findings of the FDA review of efficacy are found in the table below. Detailed findings may be found in Appendix E at the end of this review.

FDA Evaluation of Response and Clinical Benefit Claims by Applicant

Study 414

Patient No.	Blinded Period OR?	Correct Dose?	Duration [3] 28 days	Response Comment	Reviewer Response Analysis [1]	Patient Palliative Goal [2]	P.I. Palliative Goal [2]	Preventive Goal Met?	Reviewer Benefit Assessment
PATIENTS WITH BOTH CLINICAL BENEFIT AND OBJECTIVE RESPONSE PER APPLICANT'S ANALYSIS									
1797	Yes	See dosing table	Yes	Many incorrect doses	R*	None selected	None selected	Achieved	No Clinical Benefit
1825	Yes	Yes	25 d	Small lesions+measurement error+high gel/tumor ratios	No valid response	3 – no Δ	1 – 1 pt. Δ	None Selected	One point
1993	Yes	See dosing table	27 d	Missing tumor dimensions; early PD; photos incorrect	R**	1 – 1 pt. worse	None Selected	Achieved	No Clinical Benefit
1995	Yes	See dosing table	Yes	Incorrect doses (reflux)	R*	None Selected	None Selected	Achieved	No Clinical Benefit
1998	No	See dosing table	Yes	Missing tumor dimensions; DOR outside blinded phase	R **	1 – no Δ	None Selected	Achieved	No Clinical Benefit
2136	Yes	See dosing table	Yes	Both doses incorrect; many additional tumors	R*	5 – no Δ	1 – no Δ	Achieved	No Clinical Benefit
5036	Yes	See dosing table	Yes	Dosing logic unclear	R*	1 – no Δ 1 – 1 pt. worse	1 – no Δ 1 – 1 pt. worse	Achieved	No Clinical Benefit
5134	No	See dosing table	No	One dose significantly incorrect; Missing tumor dimensions	R**	1 – 3 pt. Δ 1 – 2 pt. Δ 2 – no Δ	1 – 3 pt. Δ 2 – 1 pt. Δ	Achieved@ censoring	**Apparent Clinical Benefit**
5301	Yes	Yes	Yes		**Valid Response**	2 – no Δ	1 – no Δ	Achieved@ censoring	No Clinical Benefit
5303	Yes	See dosing table	Yes	2 small dosing error + 1 significant small measurement error; high gel/tumor ratios	R**	1 – 2 pt. Δ (?PEG) 3 – no Δ	5 – no Δ	Achieved@ censoring	**Possible[3] Clinical Benefit**

[1] R* = response with errors in dosing
R** = possible response, with questions regarding tumor measurement irregularity (under discussion between FDA and Applicant)

[2] The conventions used in these columns are as follows. The first numeral refers to the number of treatment goals chosen by the patient or investigator. The next characters following the dash refer to how many points change there is in the positive direction. Thus, '5 – no Δ' indicates that there were five treatment goals chosen and there were no changes in any of them at during the study. '1 – 3 pt. Δ' indicates that there was one treatment goal chosen which revealed a three point improvement based on the scale referred to earlier in this review.

[3] The validity of these data are under discussion with the Applicant.

Patient No.	Blinded Period OR?	Correct Dose?	Duration ³ 28 days	Response Comment	Reviewer Response Analysis[1]	Patient Palliative Goal	P.I. Palliative Goal	Preventive Goal Met?	Reviewer Benefit Assessment
PATIENTS WITH OBJECTIVE RESPONSE ONLY PER APPLICANT'S ANALYSIS									
1772	Yes	See dosing table	No	Many incorrect doses	R*	No Claim	--	--	--
1992	Yes	Yes	No		No valid response	No Claim	--	--	--
2000	Yes	See dosing table	Yes	Many incorrect doses	R*	No Claim	--	--	--
2110	Yes	Mostly	Yes		**Valid Response**	No Claim	--	--	--
4964	Yes	See dosing table		Biologically unusual behavior	R **	No Claim	--	--	--
5110	Yes	Yes	No		No valid response	No Claim	--	--	--
5111	Yes	See dosing table	Yes		R*	No Claim	--	--	--
5133	Yes	See dosing table	Yes		R*	No Claim	--	--	--
5151	Yes	See dosing table	Yes		R*	No Claim	--	--	--
5348	No	See dosing table	No	No measurements after d41	R**	No Claim	--	--	--
5372	Yes	Close	Yes		**Valid Response**	No Claim	--	--	--

[1] R* = response with errors in dosing
R** = possible response, with questions regarding tumor measurement irregularity (under discussion between FDA and Applicant)

Patient No.	Blinded Period OR?	Correct Dose?	DOR ³ 28 days	Response Comment	Reviewer Response Analysis[1]	Patient Palliative Goal	P.I. Palliative Goal	Preventive Goal Met?**	Reviewer Benefit Assessment
CLINICAL BENEFIT CLAIM ONLY									
1795	No Claim	--	--	--	--	None selected	None selected	Yes	No Clinical Benefit
1871	No Claim	--	--	--	--	5 – no Δ	None selected	Yes	No Clinical Benefit
1944	No Claim	--	--	--	--	1 – no Δ	None selected	Yes	No Clinical Benefit
1996	No Claim	--	--	--	--	None selected	None selected	Yes	No Clinical Benefit
2015	No Claim	--	--	--	--	3 – no Δ	None selected	Yes	No Clinical Benefit
2157	No Claim	--	--	--	--	1 – 1 pt. Δ	2 – no Δ 1 – 1 pt. Δ	Yes	One Point
2183	No Claim	--	--	--	--	1 – no Δ	1 – 1 pt. worse 1 – 2 pt. worse	Yes	No Clinical Benefit
5253	No Claim	--	--	--	--	None selected	None selected	Yes	No Clinical Benefit
5278	No Claim	--	--	--	--	None selected	None selected	Yes	No Clinical Benefit
5396	No Claim	--	--	--	--	3 - no Δ 2 – 1 pt. worse	3 - no Δ 1 – 1 pt. worse 1 – 1 pt. better	Yes @ censoring	One point

[1] R* = response with errors in dosing
R(**) = possible response, with questions regarding tumor measurement irregularity (under discussion between FDA and Applicant

[2] The conventions used in these columns are as follows. The first numeral refers to the number of treatment goals chosen by the patient or investigator. The next characters following the dash refer to how many points change there is in the positive direction. Thus, '5 – no Δ' indicates that there were five treatment goals chosen and there were no changes in any of them at during the study. '1 – 3 pt. Δ' indicates that there was one treatment goal chosen which revealed a three point improvement based on the scale referred to earlier in this review.

The applicant determined that 21 of the 62 patients (34%) on the CEG arm had an objective tumor response. The final FDA analysis of response rate will be performed after further discussions with the applicant, and prior to the ODAC meeting on September 10. The tables above list some of the problems that FDA found in review of the data. Dosing irregularities were observed with most patients, usually because of errors in recalculating the dose after change in tumor size. In several patients, duration of response was not well documented or was only documented after the blinded phase of study. Some tumor measurement data were not recorded, perhaps because the investigator could not measure the tumor due to local tissue changes from CEG. From the data in the tables above, it seems likely that the final FDA analysis of objective response will be at least 19% (12/62) and perhaps as high as 27% (17/62) after the Applicant clarifies issues related to tumor measurements and response duration. Another issue that should be considered is how the dosing errors affect the conclusions one can draw from the study -- can we assume that when patients are given CEG according to dosing in the proposed drug labeling they will get similar results?

Clinical benefit was assessed from a palliative scale and by a preventive goal. The palliative scale, appended to this review, was used by both the patient and the investigator. Each participant could choose one or more palliative "treatment goals" which they would like to improve over the course of the study by the administration of the study drug and were obligated to designate one as the "primary" treatment goal. This primary treatment goal would comprise the primary clinical benefit data upon which the results of this goal that would be correlated with the tumor response leading to the claim of a "symptomatic response".

A preventive goal could be designated only by the investigator. Much of the clinical benefit claimed for CEG rests on preventive data. There are two significant problems with these data:

- During protocol development, FDA expressed reservations about use of preventive goals, and emphasized that it was the sponsor's responsibility to assure that specific goals were legitimate, e.g., that in the absence of effective treatment, the event that one was attempting to prevent would almost certainly occur within 28 days. FDA reviewers are not convinced that the preventive goals outlined in the NDA fulfill this requirement.
- Even more significant, FDA statistical analysis (Table 14 in FDA statistical review) suggests that the results in favor of CEG on preventive goals are artifacts of bias. Patients on the placebo arm dropped out of the study earlier (probably due to progression or lack of response) and therefore were not on study for the requisite 28 days to be declared a "success." The analysis was not driven by actual failures (e.g., skin breakthough) on the placebo arm, but rather by the tendency for patients on the placebo arm to drop out sooner. (Actually, 4 patients on CEG and 0 patients on placebo failed by having the event that was to be prevented). One should also consider the effect of these data on the sponsor's analyses of the correlation between clinical benefit and

objective response. These preventive data should be excluded from such analyses.

For the reasons discussed above, FDA does not include preventive goals as evidence of clinical benefit.

Another important issue involves the palliative treatment goals. These goals were selected by the patient, the investigator or both. They were assessed by a four-point scale designed to reflect symptoms from head and neck cancer. An important issue that remains unresolved is *what change on this scale constitutes significant clinical benefit*? The reader is encouraged to evaluate the scale in the appendix of this review to assess whether a 1-point change seems clinically relevant. The FDA analysis presents two sets of results, either including or excluding 1-point changes as clinical benefit. All changes are required to last for at least 28 days. As shown in the tables above, most of the claimed benefit was from preventive goals. Even if one includes 1-point changes as benefit, only 8% (5/62) have palliative benefit demonstrated in this study. If one excludes 1-point changes, only 3% (2/62) have documented palliative benefit.

Reviewer comment: These findings suggest IntraDose® produces limited anti-tumor activity and no significant clinical benefit has been documented in the enrolled population. Although a lesion may decrease in size or completely disappear, clinical benefit from such shrinkage cannot necessarily be assumed. The findings have implications for future trials of local therapy in the refractory/relapsed head and neck squamous cell carcinoma setting.

1.1.5 Evaluation of Safety

1.1.5.1 Deaths

Of the 110 patients who were enrolled on this study, 12 (10.9%) expired while on protocol. Analysis of the cases in which a detailed review was conducted by the medical reviewer indicated systemic disease progression to be responsible in most cases.

The applicant notes that the majority of deaths, which occurred after the patients terminated the study, were due to disease progression. The applicant also states that no deaths were related to therapy.

The medical reviewer confirms that there were no cases of immediate death directly related to injection of active or placebo CEG.

1.1.5.2 Serious Adverse Events

Serious adverse events include systemic AE's, organ-specific AE's and 'severe' local toxicity (unique for this application).

One of the most serious adverse events, stroke, was experienced by six patients on this study in the early phase of accrual. The underlying mechanism was not positively identified by the sponsor and its consultants at the time the problem initially emerged. Factors potentially predisposing patients to stroke were incorporated into the protocol as exclusion criterion. Since institution of such exclusions, there was one additional recorded case of stroke.

The applicant briefly described its experience with this serious finding. Careful analysis of the ACCESS table 'ame' was performed and confirm there were no additional cases of stroke beyond the additional one which may have been encoded using different terminology.

1.1.5.3 Analysis of Local Toxicity

Local toxicity data represented a significant component of this study and detailed information was collected by the applicant. A grading scale was used based on numbers ranging from zero to three; zero being no toxicity and three being 'severe'.

Numerical data grading the toxicity were collected at each visit for the various manifestations of the local toxicity. These manifestations included *bleeding/hemorrhage*, *erosion*, *erythema*, *eschar/scabbing*, *necrosis*, *swelling* and *ulceration*. The objective criteria by which each form of toxicity was graded were not described in the protocol.

The blinded phase of the study consisted of a minimum of three and a maximum of six administrations of study agent.

1.1.5.4 Analysis of Systemic Toxicity

Table 'ame' lists approximately 2200 adverse events reported by investigators. Although the applicant had agreed to use the NCCOG/NCI scale of toxicity (1991 edition), the majority of data collected was neither organized graded by this scale. Instead, a more subjective scale, categorized by COSTART terminology and using 'mild', 'moderate', and 'severe' to grade severity and 'not related', 'possibly related', 'probably related' and 'related' to describe attribution was employed. Objective criteria by which the reviewer could confirm the nature, severity and attribution of the AE were not provided. Therefore, the investigator's judgement at each clinical site was the primary determinant of the severity and attribution of each AE.

The medical reviewer briefly reviewed the electronic data tables pertaining to serum chemistry and hematology (Access tables 'serum' and 'hema'). There were no obvious effects on serum chemistry or hematological parameters referable to platinum administration. Neutropenia, thrombocytopenia, elevated creatinine or BUN appear to be absent. These findings suggest that IntraDose®, as administered in this study, has marginal effects on the bone marrow and kidneys.

A number of confounding variables render a quantitative analysis of the toxicities arising from active CEG (versus the placebo gel) extremely difficult. These factors include the disparity of treatment compliance and drop-off across arms, incorrect dosing (numerous examples provided), investigator differences in recording, and lack of use of standardized toxicity tables.

Brief and exploratory analysis of the relative number of AE's between arms suggests there were approximately two-fold more AE's of all types and attributions in the CEG arm. This same ratio was similar in the most important subsets, which were 'severe', and 'moderate' AE's which were 'related' and 'probably related'.

1.1.5.5 Safety Summary

There were no treatment-related deaths although six strokes were observed in the active CEG arm. The finding of stroke resulted in a modification of the administration procedure for active CEG such that tumors in the near vicinity of the carotid artery were excluded from receiving drug. There was one additional stroke following this protocol modification, suggesting the added cautions instituted were effective.

The most common reason for study termination was progressive disease.

Local toxicity was more significant in the active CEG arm compared to placebo in all the categories recorded.

Systemic AE's were more common in the active CEG arm versus placebo by a ratio of approximately two.

E. Efficacy Conclusions

Study 414 was a placebo-controlled, randomized, prospective clinical trial comparing active CEG to placebo gel in a 2:1 ratio. It was conducted in the US and Canada and enrolled 110 patients. The arms were reasonably well balanced with regard to age, gender, prior treatment, performance status, histological grade and ethnicity.

The primary efficacy endpoint was clinical benefit, and objective response was an important supportive endpoint. The clinical benefit was determined by both patient and the investigator each of whom selected and graded a variable number of 'palliative treatment goals'. The investigator, independently, also selected and evaluated one 'preventive treatment goal'. The response rate was determined by standard medical oncology criteria based on tri-dimensional measurements.

The applicant determined that of the 62 patients enrolled on strata 1 and 2 (all identified tumors as most troublesome with a volume less than 20 cm3), 21 were observed to meet the criteria for a PR or CR. Additionally, 21 of the 62 were found to have achieved 'clinically benefit' based on their scores of the treatment goals. The applicant also claimed that there were 10 of the 62 patients who met the criteria for both a response and clinical benefit.

The final FDA analysis of tumor response rate will be performed after further discussions with the applicant, and prior to the ODAC meeting on September 10. Preliminary assessment suggests that the FDA objective response rate will be between 19% and 27%. FDA analysis of clinical benefit rejected the data on preventive goals both because of treatment-related bias and because of questions

regarding the legitimacy of the preventive goals. The documented rate of clinical benefit is 8% if one includes 1-point changes in the palliative scale and is 3% if one accepts only changes of 2-points or greater in the scale. Either analysis suggests that inadequate evidence of clinical benefit has been documented in this trial.

2. Study 514-92-2

A Randomized Double-Blind, Placebo Controlled Study to Evaluate the Effect of Cisplatin/Epinephrine Injectable Gel (Product MPI 5010) When Administered Intratumorally for Achievement of Treatment Goals in Recurrent or Refractory Squamous Cell Carcinoma of the Head and Neck

2.1 Location of information reviewed in NDA:

Study Item	Volume
Study Report	4.42, 4.193
Protocol	4.21
CRF's	electronically submitted in .pdf
Database documentation	Access database '514'
Integrated Summary of Efficacy	4.164, pp. 111-225

2.2 Important Study Dates

Study Period	21 Jun 95 – 22 Mar 00
First Patient's First Treatment	28 Jun 95
Last Patient's First Treatment	11 Jan 00

2.3 Review of the protocol and amendments

Please see Appendix A for medical officer summary and comments on study protocols and amendments.

2.4 Analysis of Study 514

2.4.1 Details of Trial Conduct and Analysis

This was a 28-center study conducted in Europe and Israel with 115 patients randomized. The data submitted to the FDA are derived from patients who were enrolled between 21 June 1995 and 22 March 2000.

The sponsor states that the investigators were responsible for ensuring that the study was conducted according to Good Clinical Practices found in 21 CFR 50, 56 and 312; in accordance with Guidelines for the Monitoring of Clinical Investigations, January 1988; and also under the SOP's of the sponsoring company. All regulatory, institutional, privacy and IRB obligations were the responsibility of the investigators (v. 21, p. 44). In addition, all clinical trials were conducted according to the ethical principles of the Declaration of Helsinki (v. 21, p. 34).

The sponsor also describes in summary form many deviations from the protocol (v. 42, pp. 91-92).

2.4.2 Baseline Patient Characteristics

The following table shows the number of patients enrolled on to each stratum and arm of study 514.

	Active CEG	Placebo Gel
Stratum 1 (n=48)	31	17
Stratum 2 (n=44)	26	18
Stratum 3 (n=23)	17	6
Strata 1 & 2 only (n=92)	57	35
Total (by arm)	74	41
Study Total (both arms)	115	

One hundred fifteen patients were enrolled by 27 investigators (v. 42, p. 87). All patients received treatment with either active or placebo gel. Baseline demographics reveal that 24 (21.8%) were women and 91 (79.1%) were men. The distribution by gender is shown below.

Stratum 1 (n=48)

	Active CEG n=31	Placebo Gel n=17
Men	21	13
Women	10	4

Stratum 2 (n=44)

	Active CEG n=26	Placebo Gel n=18
Men	24	17
Women	2	1

Stratum 3 (n=23)

	Active CEG n=17	Placebo Gel n=6
Men	13	3
Women	4	3

Ethnic representation, submitted in the electronic database (Access table ‘demog’), described all patients in study 514 as ‘white’.

Ethnic Identification	Active CEG n = 74		Placebo Gel n = 41	
White	74	100.0%	100.0%	41
Black	0	0%	0%	0
Hispanic	0	0%	0%	0
American Indian	0	0%	0%	0
Asian	0	0%	0%	0

These values agree with the sponsor (Section 11.2.1.1, p. 92 and Tables 11-1 and 11-2, p. 93, v. 42).

The age at enrollment ranged from approximately 37 to approximately 84 years of age with a median of approximately 59 years (Access table 'demog').

Age	Active CEG		Placebo Gel	
	Stratum 1 n=31	Stratum 2 n=26	Stratum 1 n=17	Stratum 2 n=18
Range	37 - 82	41 - 81	46 – 84	43 - 81
Median	54	62.5	60	64

The values essentially agree with sponsor's reported results (Section 11.2.1.1, p. 92 and Tables 11-1 and 11-2, v. 42, p. 93).

The Karnofsky Performance Status at enrollment ranged from 50 to 100 with a median of approximately 80 years. (Access table 'krnfsky'). The following table shows the distribution between arms and strata.

KPS	Active CEG		Placebo Gel	
	Stratum 1 n=31	Stratum 2 n=26	Stratum 1 n=17	Stratum 2 n=18
Range	50 – 100	50 – 100	60 – 100	40 – 100
Median	90	80	90	80
Mean	85	70	81	75

The values essentially agree with sponsor's reported results (Table 11-3, p. 95, v. 42).

Histopathological data was derived from the submitted electronic database (ACCESS table 'tumorscr'). The key to the numerical representation of the histopathological grade is shown below the table. Although 92 patients assigned to strata 1 and 2 were randomized between active CEG and placebo, there were only 38 and 28 (total of 66) descriptions of histological grade included in the table 'tumorscr' respectively.

Histopathology	Active CEG		Placebo Gel	
	Stratum 1 n=21	Stratum 2 n=17	Stratum 1 n=12	Stratum 2 n=16
Range	1.0 - 3.0	1.0 - 3.0	1.0 - 3.0	1.0 - 3.0
Median	2.0	2.0	2.0	2.0
Mean	2.0	2.1	2.2	2.2

Key to Histopathology Scores:

Well differentiated	**1.0**
Moderate to well differentiated	**1.5**
Moderately differentiated	**2.0**
Moderate to poorly differentiated	**2.5**
Poorly differentiated	**3.0**

Reviewer comment: There do not appear to be appreciable differences in histopathological grade that were reported between the arms or strata. The applicant did not perform this analysis.

2.4.2.1 Prior Therapy

Prior therapy for head and neck cancer in this study included surgery, radiotherapy, chemotherapy and possibly other local therapy such as Nd:YAG or CO2 laser treatments for local ablation.

Prior Therapy	**Active CEG**					
	Stratum 1 n=31			Stratum 2 n=26		
MODALITY	S	R	C	S	R	C
Surgery (S)	1	13	0	0	8	0
Radiotherapy (R)	--	4	7	--	4	3
Chemotherapy (C)	--	--	1	--	--	0
All 3 Modalities	4			7		
UNCLEAR	0			2		

Reviewer comment: These values vary from those found in the sponsor's analysis (v. 42, p. 96). The sponsor states that 10 patients in stratum 1 of the active arm received all three modalities compared to 4 in the FDA analysis.

Prior Therapy	Placebo Gel					
	Stratum 1 n=17			Stratum 2 n=18		
MODALITY	S	R	C	S	R	C
Surgery (S)	0	3	0	0	8	0
Radiotherapy (R)	--	4	2	--	3	4
Chemotherapy (C)	--	--	0	--	--	0
All 3 Modalities	7			6		
UNCLEAR	1			0		

2.4.3 Therapy Delivered

The ITT population of all 115 patients in this study is used in the FDA analysis of therapy delivered. Detailed review of the claimed responders and clinical benefitters suggests that compliance after the first few visits drops significantly.

# of Treatments Received	**Active CEG** n = 57	**Placebo** n = 35
1	57 (100.0%)	35 (100.0%)
2	55 (96.5%)	30 (85.7%)
3	49 (86.0%)	24 (68.6%)
4	34 (59.6%)	15 (42.9%)
5	24 (42.1%)	8 (22.9%)
6	24 (42.1%)	6 (17.1%)

2.4.3.1 Termination

Review of the table 'studycomp' indicates the reasons patients were terminated from the study. The following table below indicates the relative frequencies of the various reasons for termination:

Reason for Termination	Number (%)
Systemic disease progression	22 (19.1)
Progressive disease of the target tumor	44 (38.2)
Patient request, not otherwise specified	9 (7.8)
Unacceptable adverse events/local toxicity	9 (7.8)
Death on study	13 (11.3)
Need for other therapy not per protocol	2 (1.7)
Completed study	6 (5.2)
Other:	10 (8.7)
"Re-treatment with open label"	1
"No convincing response"	2
"Investigator decision"	1
"Deterioration of Karnofsky status"	1
"Incomplete regression"	1
"Pharmacy error"	1
Lost to follow-up	1
"Responsive of treated tumor [sic] tumor 1"	1
"Changed to open label at treatment #5"	1
Total	115 (100.0)

The principal results agree closely with the applicant's analysis. The Study Report (v. 15, p. 88) states that 44% of patients discontinuing study participation for local or systemic disease progression. Slight differences may be noted in the other reasons for study terminations from Tables 10-3 and 10-2 (v. 15, p.90-91) when compared to this table, but they are not of significant magnitude to affect the overall results of this study.

2.4.4 Evaluation of Efficacy

2.4.4.1 Sponsor's Evaluation of the Primary Efficacy Endpoint

The applicant claims an objective MTT response (CR or PR) in the blinded phase of 25% (14/57) patients randomized to strata 1 and 2 of active CEG (Table 11-10, v. 42, pp. 100-101). The sponsor also claims one MTT objective response (1/35) in the placebo arm.

The applicant also claims a clinical benefit in 19% (11/57) of patients randomized to the active CEG arm (including both strata 1 and 2) (Section 11.4.1.2.2 and Table 11-20, v. 42, p. 110-111).

The applicant has examined the association between MTT response and clinical benefit and finds that 43% (6/14) of patients who achieved an MTT response (during the blinded phase) also achieved a clinical benefit.

Using the applicant's claimed rate of blinded phase MTT response and rate of clinical benefit, the following table may be constructed:

Study 514		MTT Blinded Phase Objective Response with Active CEG?		Total with Active CEG
		Yes	No	
Clinical Benefit with Active CEG?	Yes	6	5	11
	No	8	38	46
Total with Active CEG		14	43	57

Reviewer comment: The table above suggests that there may be a correlation between a blinded phase MTT objective response and clinical benefit. This table is similar to one produced by the sponsor (Table 11-23, p. 117). By FDA analysis, chi-square analysis reveals $\chi^2 = 6.14$ (df=1, p=0.010) which suggests statistical significance.

2.4.4.2 Medical Officer's Evaluation of the Primary Efficacy Endpoints

See the FDA review of efficacy of Trial 414 for a detailed discussion of the FDA approach to review of efficacy. The following is the medical reviewer evaluation of response and clinical benefit. Efficacy data from each of the objective or clinical benefit responses claimed by the applicant were carefully reviewed to evaluate adherence to the protocol and data quality. A summary of the findings of the FDA review of efficacy are found in the tables below.

FDA Evaluation of Response and Clinical Benefit Claims by Applicant

Study 514

Patient No.	Blinded Period OR?	Correct Dose?	DOR ³ 28 days	Response Comment	Reviewer Response Analysis[1]	Patient Palliative Goal[2]	P.I. Palliative Goal[2]	Preventive Goal Met?	Reviewer Benefit Assessment
CLINICAL BENEFIT AND RESPONSE CLAIM									
2687	Yes	Yes	Yes	Biologically unusual; SD x 63d, then unexpected CR at d103-132 Substantial weight loss	**Response valid**	1 – 1 pt. Δ	1 – 1 pt. Δ	None Selected	One point
2688	Yes	Yes	No		No valid response	1 – 1 pt. Δ	1 – 1 pt. Δ	None Selected	One point
2732	Yes	See dosing table	Yes	All three doses incorrect; Missing tumor dimensions	R**	None Selected	1 – 3 pt. Δ 1 – 2 pt. Δ	None Selected	**Apparent Clinical Benefit**
2735	No	See dosing table	Yes	Missing tumor dimensions; Inevaluable dosing regimen	R**	1 – 1 pt. Δ	1 – 1 pt. Δ	None Selected	One point
2736	Yes	See dosing table	Yes	Missing tumor dimensions; Substantial weight loss	R**	1 – 1 pt. Δ	1 – 1 pt. Δ	None Selected	One point
5854	Yes	Yes	Yes		**Response valid**	1 – 2 pt. better 4 – no Δ 1 – 1 pt. worse	1 – 1 pt. worse	Achieved @ censoring	No Clinical Benefit

[1] R* = response with errors in dosing
R** = possible response, with questions regarding tumor measurement irregularity (under discussion between FDA and Applicant)

[2] The conventions used in these columns are as follows. The first numeral refers to the number of treatment goals chosen by the patient or investigator. The next characters following the dash refer to how many points change there is in the positive direction. Thus, '5 – no Δ' indicates that there were five treatment goals chosen and there were no changes in any of them at during the study. '1 – 3 pt. Δ' indicates that there was one treatment goal chosen which revealed a three point improvement based on the scale referred to earlier in this review.

Patient No.	Blinded Period OR?	Correct Dose?	DOR ³ 28 days	Response Comment	Reviewer Response Analysis[1]	Patient Palliative Goal	P.I. Palliative Goal	Preventive Goal Met?	Reviewer Benefit Assessment
RESPONSE CLAIM ONLY									
2541	No	Yes	No	Only one dose administered	No valid response	No Claim	--	--	--
2681	Yes	Yes	Yes	Many incorrect doses < 10% off	**Response valid**	No Claim	--	--	--
2686	Yes	Yes	Yes	One incorrect dose	**Response valid**	No Claim	--	--	--
2731	Yes	See dosing table	Yes	Many incorrect doses	R*	No Claim	--	--	--
2753	Yes	Yes	Yes	Close; within 12%	**Response valid**	No Claim	--	--	--
5494	Yes	See dosing table	27d	Many incorrect doses	R*	No Claim	--	--	--
5496	Yes	See dosing table	Yes	Many incorrect doses	R*	No Claim	--	--	--
5565	Yes	Yes	Yes		**Response valid**	No Claim	--	--	--

[1] R* = response with errors in dosing
R** = possible response, with questions regarding tumor measurement irregularity (under discussion between FDA and Applicant)

Patient No.	Blinded Period OR?	Correct Dose?	DOR ³ 28 days	Response Comment	Reviewer Response Analysis[1]	Patient Palliative Goal[2]	P.I. Palliative Goal[2]	Preventive Goal Met?	Reviewer Benefit Assessment
CLINICAL BENEFIT CLAIM ONLY									
2366	No Claim	--	--	--	--	2 – 1 pt. Δ	1 – no Δ 1 – 1 pt. Δ	None Selected	One point
2421	No Claim	--	--	--	--	1 – 1 pt. Δ 1 – no Δ	1 – no Δ	None Selected	One point
2564	No Claim	--	--	--	--	1 – 1 pt. Δ	1 – 1 pt. Δ	None Selected	One point
5421	No Claim	--	--	--	--	1 – 1 pt. Δ 1 – no Δ	2 – 1 pt. Δ	None Selected	One point
5588	No Claim	--	--	--	--	1 – 1 pt. Δ worse	None Selected	Failed	No Clinical Benefit

[1] R* = response with errors in dosing
R** = possible response, with questions regarding tumor measurement irregularity (under discussion between FDA and Applicant)

[2] The conventions used in these columns are as follows. The first numeral refers to the number of treatment goals chosen by the patient or investigator. The next characters following the dash refer to how many points change there is in the positive direction. Thus, '5 – no Δ' indicates that there were five treatment goals chosen and there were no changes in any of them at during the study. '1 – 3 pt. Δ' indicates that there was one treatment goal chosen which revealed a three point improvement based on the scale referred to earlier in this review.

The applicant determined that 14 of the 57 patients (25%) on the CEG arm had an objective tumor response. The final FDA analysis of response rate will be performed after further discussions with the applicant, and prior to the ODAC meeting on September 10. The tables above list some of the problems that FDA found in review of the data. Dosing irregularities were observed with most patients, usually because of errors in recalculating the dose after change in tumor size. FDA rejects two of the responses as having inadequate documenation of the required 28-day response duration. In three additional cases, the reason for lack of recorded tumor measurements at some visits needs to be clarified. From the data in the tables above, it seems likely that the final FDA analysis of objective response will be at least 16% (9/57) and perhaps as high as 21% (12/57) after the Applicant clarifies issues related to tumor measurements.

Another issue that should be considered is how the dosing errors affect the conclusions one can draw from the study -- can we assume that when patients are given CEG according to dosing in the proposed drug labeling they will get similar results?.

As noted in discussion of the efficacy results in Study 414, FDA did not accept preventive goals as evidence of clinical benefit. However, this had no effect on analysis of Study 514, as none of the claimed clinical benefit successes were based on preventive goals. On the other hand, the issue of whether 1-point changes on the palliative scale constitute clinical benefit does affect this analysis. If one point-changes are included as clinical benefit, the clinical benefit rate is 16% (9/57); if only 2-point and greater changes are accepted, the clinical benefit rate is only 2% (1/57).

2.4.5 Evaluation of Safety

2.4.5.1 Deaths

Of the 115 patients who were enrolled on this study, 13 (11.3%) expired while on protocol. Analysis of the cases in which a detailed review was conducted by the medical reviewer indicated systemic disease progression to be responsible in the majority of cases.

The applicant notes that the majority of deaths, which occurred after the patients terminated the study, were due to disease progression. The applicant also states that no deaths were related to therapy.

The medical reviewer confirms that there were no cases of death directly related to injection of active or placebo CEG.

2.4.5.2 Serious Adverse Events

Serious adverse events (SAE's) include severe systemic AE's and severe organ-specific AE's. Unique to this application local toxicity data that was systematically collected. Local toxicity was occasionally to frequently found to be "severe" in nature.

One of the most serious adverse events, acute stroke, was observed in six early patients in Study *414*. This finding was not observed in study 514. The underlying mechanism was not positively identified by the sponsor and its consultants at the time the problem initially emerged, although factors potentially predisposing patients to stroke were incorporated into the protocol as exclusion criterion. Since the institution of such exclusions, there was only on additional recorded case of stroke in study 414.

2.4.5.3 Analysis of Local Toxicity

Local toxicity data represented a significant component of this study and detailed information was collected by the sponsor. A grading scale was used based on numbers ranging from zero to three; zero being no toxicity and three being 'severe'.

Numerical data describing the toxicity were collected at each visit based on the several factors comprising the local toxicity. These components include bleeding/hemorrhage, erosion, erythema, eschar/scabbing, necrosis, swelling and ulceration. The objective criteria by which each toxicity was graded were not described in the protocol.

The blinded phase of the study consisted of a minimum of three treatments and a maximum of six administrations of study agent. The comparison of active CEG to placebo will only be performed up to study visit 4.

2.4.5.4 Analysis of Systemic Toxicity

The electronic database contains Access table 'ame' which lists approximately 900 adverse events reported by investigators. Although the applicant had agreed to use the NCCOG/NCI scale of toxicity (1991 edition), the majority of data collected were not graded by this scale. Instead, a less useful scale, categorized by COSTART terminology was employed. This grading system uses more subjective terms such as *mild, moderate,* and *severe* to grade severity and *not related*, *possibly related*, *probably related* and *related* to describe attribution. Objective criteria by which an independent and uninterested reviewer could reconstruct the nature, severity and attribution of the AE were not provided thereby disallowing independent confirmation of the investigators' grading and attribution selections. Essentially, the subjective opinion of the evaluator at each clinical site was the primary determinant of the severity and attribution of each AE.

Review of the tables relevant to serum chemistry and hematological toxicity by the medical officer (Access tables 'serum' and 'hema') indicates the anticipated effects of CEG on the bone marrow and kidneys (from the active moiety cisplatin) is minimal and possibly not detectable.

There are a number factors confounding a quantitative analysis of the toxicity of active CEG as it compares to placebo. These factors include the disparity of treatment compliance and drop-off across arms, incorrect dosing (numerous examples provided), investigator differences in recording, and lack of use of standardized toxicity tables.

Brief and exploratory analysis of the relative number of AE's between arms suggests there were approximately two-fold more AE's of all types and attributions in the CEG arm. This same ratio was similar in the most important subsets, which were 'severe', and 'moderate' AE's which were 'related' and 'probably related'.

2.4.5.5 Safety Summary

The finding of stroke in study 414 resulted in a modification of the administration procedure for active CEG such that tumors in the near vicinity of the carotid artery were excluded from receiving drug. There was one additional stroke in study 414 following this protocol modification, suggesting the protocol

modifications employed were effective. No strokes were observed in study 514. The most common reason for study termination was progressive disease. Local toxicity was more significant in the active CEG arm compared to placebo in all categories evaluated. Systemic AE's were more common in the active CEG arm compared to placebo by a ratio of approximately two.

D. Efficacy Conclusions

Study 514 was a placebo-controlled, randomized, prospective clinical trial comparing active CEG to placebo gel in a 2:1 ratio. It was conducted in the Europe and Israel and enrolled 115 patients. The arms were reasonably well balanced in terms of age, gender, prior treatment, performance status, histological grade and ethnicity.

The primary efficacy endpoint was clinical benefit, and objective response was an important supportive endpoint. The final FDA analysis of tumor response rate will be performed after further discussions with the applicant, and prior to the ODAC meeting on September 10. Preliminary assessment suggests that the FDA objective response rate will be between 16% and 21%. FDA analysis of clinical benefit rejected the data on preventive goals both because of treatment-related bias and because of questions regarding the legitimacy of the preventive goals. The documented rate of clinical benefit is 16% if one includes 1-point changes in the palliative scale and is 2% if one accepts only changes of 2-points or greater in the scale. Either analysis suggests that inadequate evidence of clinical benefit has been documented in this trial.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The safety evaluation of IntraDose® derives from the two pivotal studies submitted as part of NDA 21-236. These studies were prospective, randomized, double-blind, placebo-controlled clinical trials. The safety data collected included systemic AE's, local toxicity and vital signs immediately following each administration of the study drug.

Systemic toxicity data were categorized using COSTART terminology and were graded using a subjective scale of 'mild', 'moderate', or 'severe'. Attribution was assigned using the following terms: 'related', 'probably related', 'possibly related' and 'not related'. Although intended to be used in the collection of systemic safety data, the NCCOG criteria were neither used to group the AE's nor to grade their severity. The lack of standardization and objectivization of safety data represents a major flaw in the safety evaluation of IntraDose®.

In both studies, there was an approximately 2-fold excess in the number of reported systemic AE's on the IntraDose® arm as compared to the placebo arm after normalizing for the 2:1 randomization. This suggests there is more systemic toxicity associated with the use of IntraDose®. These findings were consistent in the subsets of 'moderate' and 'severe' toxicities and in the subsets 'related' and 'probably related' attribution. Direct comparison, however, is rendered difficult by a number of confounding factors including disparity in the treatment compliance between arms, investigator differences in reporting AE's, investigator differences in grading AE's and dosing inconsistencies.

There were a number systemic AE's that were extremely important and require reemphasis in this section. **Stroke**, by several possible mechanisms, was initially observed in six patients. Following an amendment to the protocol excluding tumors in close proximity to the carotid artery, one additional stroke was observed, though its relationship to study agent is unclear. **Blindness** occurred in at least one instance which the investigator rated as 'severe' and 'related' to study drug administration. This patient was randomized to IntraDose®.

Local toxicity data was collected in a very careful manner by the investigators. Manifestations of local toxicity graded included eschar formation, ulceration, erosion, necrosis, bleeding, swelling and erythema. Each manifestation was graded each visit on a scale of 0-3 (with 0=none, 1=mild, 2=moderate and 3=severe). No objective criteria were included by which these toxicities could be graded and thus their grading relied on the subjective interpretation of the investigators. Because of this effort, a very clear picture of the way each local toxicity varied over time under continued study drug administration or following drug administration.

Each toxicity could be observed varying over time during and after study drug administration in each individual patient. The smoothness of many of the curves suggested that, for a single patient and investigator, the internal consistency was quite high. Across different investigators, however, the medical reviewer cannot be confident about the inter-observer variability. The results indicate that patients' most troublesome tumors are very heterogeneous in their physical presentation, growth characteristics and complications they cause in the host based on their location, size, and relative invasiveness. Additionally, there remains remarkable heterogeneity in the study subjects' cutaneous reaction to the injected gel with some patients experiencing moderate toxicity in 2 or 3 parameters while others experienced severe toxicity in 5 or more of the same parameters.

The last toxicity specifically monitored for was an allergic type reaction immediately following the injection of study drug. Vital signs were collected every 5 minutes. The results indicate that a very small fraction of the patients receiving active or placebo gel experienced clinically significant diminutions in systolic and/or diastolic blood pressures.

B. Additional Safety Studies or Specific Findings in the Safety Review

Studies 414 and 514 comprised the vast majority of the clinically relevant safety database and are the principal data sources for the toxicity analyses performed for this NDA review. Studies 39-93-P, 403-93-2 and 503-93-2 were small phase 1 or II studies in substantially different patient populations. The sites of injection, volume of injected material, toxicity data collection methods and natural history of the various solid tumors represented in this studies renders their safety data substantially incomparable to the safety databases represented by studies 414 and 514.

C. Adequacy of Safety Testing

Safety testing of IntraDose® was, by the medical officer's estimate, adequate in this application. The data submitted provides a reasonable degree of confidence of the anticipated safety events and their frequency. Unique to this application was the thorough and systemic evaluation of, grading of and recording of a large body of toxicity in the local area of the tumor(s) injected. The applicant is to be specifically commended on the superlative effort expended by itself and its investigators.

E. Summarize Critical Safety Findings and Limitations of Data

Should IntraDose® become approved for its proposed indication of recurrent squamous cell head and neck cancer, there remains concern about the product causing stroke and/or blindness, both of which were observed in controlled studies. Additionally, the appearance local toxicity confounds measurement of the tumors' dimensions rending dose calculations difficult or incorrect. This has implications as to whether patients will be receiving the approved dose and schedule.

VIII. Dosing, Regimen, and Administration Issues

The dose and schedule of administration of IntraDose® studied in the two pivotal trials (Studies 414 and 514) was amended during accrual. This change lead to early patients receiving a different dosing regimen administered by a different technique than later patients. The statistical reviewer noted a relationship, in an exploratory *post hoc* analysis, that suggests the optimal dose may be difficult to determine without careful testing in a new study. The data from one study indicate that the lower dose could confer a higher tumor response rate whereas data from the other study suggests the opposite (please refer to the statistical review for more details).

There were numerous errors in dosing and administration of both dosing regimens documented in each study. These are more fully described in the "Dosing Tables" which combine the tumor dimension data and dosing data for each patient visit. These data suggest that calculation of the correct dose of IntraDose(R) represents a substantial obstacle to safe and effective use of this product. Moreover, the difficulty of carefully measuring – with out addressing precision and/or reproducibility -- individual tumors in the absence of an imaging modality presents grave potential for incorrect dosing by practitioners.

A dose-response relationship has not been established for this product. An unplanned dosing regimen change during the study period resulted in an approximate two-fold difference in dose. The two doses appear to be tolerable and approximately equally effective.

The reviewing clinical pharmacologist has expressed concerns about the validity of the claim by the applicant that this formulation of cisplatin retains the active and toxic platinum species intratumorally and in high concentrations. Analysis of the pharmacokinetic data from Study 516-99-PK indicates that intratumoral administration, on a dose-normalized basis, resulted in circulating *systemic* levels similar to that of intravenously-administered cisplatin.

Based on the mid-study change in dosing regimen and technique, frequent errors in the calculations of tumor volume and dose observed, lack of a clear dose-response relationship and lack of local high platinum retention, as claimed, suggest full

pharmacological evaluation of this product has not been achieved. The reviewing medical officer's confidence about the applicant's proposed dosing regimen is limited.

IX. Overall Summary

In the mid-1990s, FDA and the Applicant held numerous meetings to discuss how one might design a trial to document the clinical benefit associated with local treatment of incurable head and neck cancer. FDA's position was that shrinkage of tumors from local injection of chemotherapy was not sufficient evidence of clinical benefit. Any treatment, including local treatment, was likely to produce some side effects, and nobody had proved that temporary shrinking of head and neck cancer yielded any benefit that the patient could perceive. One of the difficulties encountered was that head and neck cancer patients suffer many different problems, so that it would be impossible to accrue enough patients to evaluate treatment of each problem separately. With FDA's concurrence, the Applicant approached this difficulty by individually documenting the nature of each patient's problem: each patient and physician were to specify in advance the main problem. The physician was to identify the tumor that was associated with that problem (MTT, most troublesome tumor). The study was to demonstrate whether the main symptomatic problem in each individual patient was improved and whether there was a strong association between symptomatic improvement and tumor response.

After reviewing the sponsor's proposal, FDA communicated two reservations about the proposed plan:

- The sponsor proposed using preventive goals as a component of clinical benefit. FDA emphasized that it was the sponsor's responsibility to assure that specific goals were legitimate, e.g., that in the absence of effective treatment, the event that one was attempting to prevent would almost certainly occur within 28 days. FDA reviewers are not convinced that the preventive goals outlined in the NDA fulfill this requirement.
- The sponsor proposed that using the proposed 4-point symptom evaluation scale (see appendix E), an increase of 1-point or greater would constitute clinical benefit. The FDA noted that it was unclear whether a 1-point change would be sufficient to define significant clinical benefit for each category on the scale and that the Applicant would need to support this position. (The view of ODAC on this point would be instructive.)

Another issue addressed during these meetings was the evidence that each component of CEG contributed to safety and efficacy. On the basis of preclinical data, FDA accepted that epinephrine was contributed to the efficacy of CEG. The contribution of collagen was accepted based on its role in providing uniform mixing and delivery of cisplatin and epinephrine. (No efficacy advantage of the collagen gel was demonstrated in animals.) The role of cisplatin in providing clinical benefit was to be tested in controlled trials of CEG versus epinephrin-gel acting as a placebo control.

The two primary studies submitted in support of marketing approval in this NDA were double-blind, randomized (2:1), placebo-controlled prospective clinical trials of

approximately the same size, with about 60 patients randomized to the CEG arm in each study. Trial 414 was performed in the US and Trial 514 was performed in Europe. The primary efficacy endpoints in each study were clinical benefit and tumor response.

In both the FDA and the Applicant's analyses of efficacy, a low to moderate rate of tumor shrinkage and objective response is noted. FDA's final objective response rate (ORR) will depend on further clarification of the data by the sponsor, but the following table presents the range of likely findings in patients on the CEG arm of the two trials:

	Applicant ORR	**FDA ORR**
Trial 414	34% (21/62)	19% (12/62) to 27% (17/62)
Trial 514	25% (14/57)	16% (9/57) to 21% (12/57)

However, FDA and Applicant findings on clinical benefit (CB) differ substantially as indicated below. FDA results differ according to whether 1-point changes (1-PC) on the symptom scale are included as clinical benefit:

	Applicant CB	**FDA CB** (Excluding 1-PC)	(Including 1-PC)
Trial 414	34% (21/62)	3% (2/62)	8% (5/62)
Trial 514	19% (11/57)	2% (1/57)	16% (9/57)

The large difference between the FDA and Applicant analyses of CB in trial 414 is because most of the benefit claimed by the Applicant was from attainment of preventive goals, and FDA excluded the preventive findings. (FDA determined that the preventive findings were based on bias from asymmetric dropout of patients from the two study arms rather than from a difference in the occurrence of clinical events.)

None of the CB findings were statistically different from placebo. Final assessment of whether there is a relationship between OR and CB will be made after final FDA assessment of ORR. However, there are clearly insufficient data on CB in study 414 to make this assessment, and even if one includes 1-point changes in the FDA analysis of CB, no more than 4 patients with potential objective responses in study 514 will have documented CB. It seems very unlikely that a strong relationship between ORR and CB will be established with these data.

Another issue that should be considered is how the dosing errors affect the conclusions one can draw from the studies. In both studies, errors were made in most patients in recalculating the appropriate dose after tumor shrinkage -- can we assume that when patients are given CEG according to dosing in the proposed drug labeling they will get similar results?

IntraDose® administration is associated with moderate to severe agent-induced toxicity observed both locally and systemically. The reviewing medical officer concludes that, as evidenced by two adequate and well-controlled clinical trials, the data strongly suggest that the risk (which is generally moderate but occasionally severe) of administering IntraDose® outweighs the small clinical benefit conferred on the studied population.

B. Recommendations

The reviewing medical officer recommends against marketing approval for IntraDose® for use as proposed in the draft label pending ODAC discussion.

This recommendation is based on the finding of extremely limited efficacy and moderate to severe toxicity reproducibly demonstrated in two clinical trials specifically designed to evaluate safety and efficacy of IntraDose®.

Future trials for local therapy in this clinical setting will require careful sponsor and divisional consideration in the design of improved clinical protocols. Factors to consider in the design of forthcoming trials might include the following safety parameters: the rate and severity of local and systemic toxicities, the use of standardized toxicity criteria and uniform collection of toxicity data. Improved characterization of the heterogeneous natural history of head and neck squamous cell lesions over time would find immediate utility. Such parameters would include native growth rate, susceptibility to locally injected cytotoxic agents and non-cytotoxic material as a function of time, dose, volume, method of injection, size, location, histopathological grade and prior therapy.

XI. Appendices

A. Description and Review of Study Protocol Including Amendments
B. Table of Adverse Events (not included in the ODAC briefing document)
C. Narratives of Selected Toxicities (not included in the ODAC briefing document)
D. Regulatory History
E. Reproduction of the Palliative Treatment Goal Scale
F. Summary Tables from a Review of the Literature
G. Reproductions of the Most Relevant Publications (not included in the ODAC briefing document)

Appendix A

Description and Review of Study Protocol Including Amendments

1. Studies 414-94-2 and 514-94-2

A Randomized Double-Blind, Placebo Controlled Study to Evaluate the Effect of Cisplatin/Epinephrine Injectable Gel (Product MPI 5010) When Administered Intratumorally for Achievement of Treatment Goals in Recurrent or Refractory Squamous Cell Carcinoma of the Head and Neck (inclusive of amendments I-V)

1.1 Location of information Relevant to the Protocol for both studies:

Study Item	Volume
Protocol	4.21
CRF's	Electronically submitted
Database documentation	Electronically submitted

1.2 Review of the protocol and amendments

Amendment #1 Volume 4.21 (p.80) 03 Feb 1995 # Patients before amendment: 0

This amendment clarified a number if issues which are listed below. No patients were entered on the protocol until Amendment #3. The following trial design features were clarified:

- Study design changed to a randomized, double-blind, placebo controlled trial
- Added treatment goals as a primary study objective and primary efficacy endpoint
- Added the requirement for an identifiable treatment goal as an entry criterion
- Clarified restrictions of concomitant therapy
- Clarified Treatment Plan for patients who are treatment failures
- Added minimum tumor volumes and minimum does per tumor required for inclusion in the efficacy analysis
- Specified minimum dose for tumors that may be treated but will not be included in the efficacy analysis
- Clarified Visit Schedule and Study Visit Requirements
- Replaced FACT-H&N version 2 with version 3
- Clarified primary and secondary efficacy parameters
- Revised Statistical Methods section
- Added Appendix G, Treatment Goal Questionnaire

Amendment #2 Volume 4.21 (p.80) 05 May 1995 # Patients before amendment: 0

This amendment clarified a number if issues which are listed below. No patients were entered on the protocol until Amendment #3. The following trial design features were clarified:

- Clarified the need for the local Investigator to identify the patient's MTT and a primary treatment goal related to that tumor prior to the enrollment of the patient
- Clarified that the primary efficacy endpoint will be an objective response to treatment as measured by change in tumor volume for the MTT
- Clarified that all the laboratory studies will be conducted by a designated central laboratory
- Clarified that the decision to enter a patient into open-label treatment at treatment visit 4 or beyond will be determined by disease progression (>25% increase in tumor volume) of the MTT (as identified by the investigator)
- Clarified the objective response criteria
- Add tumors involving a major artery or any visceral organ as an exclusion criterion and clarify that systemic disease in tissues such as the liver, lung, or pancreas will not receive treatment with the gel.
- Revised the Statistical Methods section of the protocol.

Amendment #3 Volume 4.21 (p.74) 25 Sep 1995 # Patients before amendment: 6

This amendment clarified a number of issues that are listed below:

- Allowed up to 30 patients with >20cm3 tumors to be enrolled. If the MTT was >20, the maximum dose of 10 mL of gel would be distributed evenly throughout the tumor. If the assigned dose for the MTT was <10mL the remaining dose volume may be distributed to additional target tumors.

Review Comment: This amended item could present unintended drug administration obstacles, although it does not influence the planned analysis of strata 1 and 2 upon which the efficacy of this agent rests. The problems with this approach is that there is potentially much heterogeneity in the dose and manner in which the MTT is treated. For larger tumors such as 25 cm3, 7.5 ml would be administered to the MTT and 2.5 mL to other lesions. The ratio of 0.25 mL of gel for each 1 ml of tumor was maintained. For a 50 cm3 tumor, the ratio would not be maintained and thus one would anticipate reduced activity.

- Guidelines were added for the treatment of total target volume in excess of 20 cm3.
- Clarify that previous cancer treatment includes any prior therapy
- Allow patient study entry within 28 days of completing previous cancer therapy with documented evidence of stable disease or disease progression and the Investigator feels that enrollment into the study would not pose any additional safety risk to the patient and the Investigator feels that enrollment into the study would not pose any additional safety risk to the patient.
- Clarify that investigational new chemical entities are prohibited in the 28 days prior to first treatment, during the Treatment Phase and during re-treatment in the Extended Follow-up Phase (6 treatments in 8 weeks, followed by weekly evaluation for 4 weeks).
- Allow concomitant medication to include radiation therapy to distant non-target metastases and stable, maintenance doses of hormonal therapy such as Megace and tamoxifen.
- Clarify that it is preferable for the MTT or another target tumor to have been biopsied for histological confirmation of malignant disease prior to study

Reviewer comment: This bullet seems to contradict a similar point in the previous amendment about confirming histological eligibility based on the initial biopsy. There is not a substantial body of literature indicating how histological grade in this setting influences prognosis or anticipated palliative benefit.

- Clarify the unit of stratification from patients total baseline tumor volume to volume of the MTT

Reviewer comment: This could be an important factor if the number of patients incorrectly stratified is large or a disproportionately large number of responding patients in this category are found.

- Delete the requirement for treatment of all tumors present at baseline

Reviewer comment: How many patients would be affected by this? Does it make a difference in the overall outcome? It appears from database 'dosing' element 'dsdsplsn' that 6 patients were enrolled before or on the date of this amendment (patients 1823, 1776, 1799, 1991, 1799, 1798).

- Clarify timepoints tumor measurement requiring imaging guidance

Amendment #4 Volume 4.21 (p.70) 13 Mar 1996 # Patients before amendment: 22

This amendment clarified a number of issues, which are listed below:

- The injection procedure was modified to require gradual administration of the CEG in increments of 2.5 mLs and monitoring of the VS at 5 minute intervals. Any clinically significant change in a patient's status during the injection procedure will require suspension of treatment until the next visit.

Reviewer comment: What was the injection procedure prior to is amendment? It could be that there was heterogeneity in the way the investigators injected CEG. If so, does this imply potential safety problems during initial use of the CEG when it first gets out on the market? Will it be necessary to monitor the VS q 5 minutes with stopping of additional injection if AE's are encountered? What exactly were the problems observed? The patients enrolled before this amendment date may be found in electronic table 'demog' in the study 414 electronic database by sorting on 'assdate'.

- The guidelines were revised for pain management during and after injection of the CEG.

Reviewer comment: What was the inciting event and what impact does this have on our ability to determine the amount of pain generated when CEG is injected?

- The use of bupivicaine was prohibited
- Guidance was provided regarding the use of local anesthetics
- Study results from 39-92-P were included in the Introduction
- Clarified that placebo gel contains sodium phosphates and sodium chloride
- Deleted Bristol's PI for Platinol to treat cancer as a side effect reference.
- Matrix's address and telephone number were changed
- The list of responsible Matrix staff was revised.

Amendment #5 Volume 4.21 (p.3) 02 May 1997 # Patients before amendment: 60

This amendment clarified a number of issues, which are listed below:

- Enrollment to stratum 3 was closed
- Patients with tumors > 20 cm3 are excluded
- Patients are excluded who have a known history of clinically significant extracranial carotid vascular disease from either atherosclerosis or radiation therapy or previous carotid surgery

Reviewer comment: These exclusions may need to appear in the labeling in a *black box* context.

- Patients were excluded with tumors that directly involved or threatened to invade the carotid artery, including any tumor in close proximity to a major vessel of the extracranial vascular system including the common, internal and external carotids or the vertebral artery.

Reviewer comment: This limits the population for which this agent is intended. The specific distance above which a practitioner might feel comfortable is not specified. This is an important point. Clearly the sponsor wishes to have the broadest applicability, but at the same time excludes a modest fraction of the population that this agent might serve. A question to our consultant might be to what degree the intended population for this agent has been so whittled down over legitimate safety concerns that its usefulness disappears.

- Reduced dosage to 0.25mL/cm3 of tumor volume during the double-blind phase

Reviewer comment: this is a 50% reduction and the efficacy of the two different amounts should be compared. Additionally, what was the underlying reason for this dose reduction? If it was concern over the volume of the injected material, then the same amount of cisplatin may be injected into the lesion by doubling its concentration in the gel. If the concern was really about the amount of the cisplatin independent of the volume, again, the concentration can be reworked to formulate a more optimal drug product. Preclinical models are only slightly helpful in this case since a clinical decision was made, ostensibly on the basis of clinical data. There is a risk of diminished efficacy. How carefully was the concentration of CDDP escalated to determine the optimal cisplatin concentration that optimizes safety and efficacy?

- Guidelines for dose re-calculation based on tumor measurements at each visit were added.

- The dosing scheme was modified to allow the dose to be escalated following the first treatment in the extended follow-up to the previous 0.5 ml/cm3 of tumor volume if the tumor progresses in size or remains stable with no cutaneous reactions.

Reviewer comment: It appears that the applicant believes that there might be more efficacy if a larger amount (vs. higher concentration) of CDDP is injected. Moreover, there appears to be a difference in the local reaction profiles between the 0.25 and the 0.5 mL/cm3. This suggests further that the sponsor did not know prior to the critical developmental studies that correct cisplatin *concentration* was known. We can address some of the safety profile questions by looking at the local toxicities in all patients. The efficacy question will be more difficult to answer because the number of responders is quite small.

- The PS eligibility criteria were changed to KPS of 60 – 100%.

- The guidance to the investigators about using imaging and interpreting the images in light of the altered anatomy prior to injecting was clarified.

Reviewer comment: This appears, also, to be a very important safety parameter to carefully consider. This suggests that imaging will probably be ordered on most or all patients and that certain findings on the imaging will be concerning enough to render CEG contraindicated. Should approval be anticipated, we must carefully, in

conjunction with the applicant, consider the information that should appear in a *black box warning* and under what circumstances CEG should be relatively and absolutely contraindicated.

- Guidelines for collection procedures for the platinum plasma assay were included
- The list of Matrix staff responsible for the protocol were revised.

1.3.1 Title

A Randomized Double-Blind, Placebo Controlled Study to Evaluate the Effect of Cisplatin/Epinephrine Injectable Gel (Product MPI 5010) When Administered Intratumorally for Achievement of Treatment Goals in Recurrent or Refractory Squamous Cell Carcinoma of the Head and Neck

1.3.2 Objectives

There were seven objectives for this study (v. 21, p. 17):

1. To compare the effect of MPI 5010 to placebo gel on the local tumor volume

2. To assess the achievement of an identified primary treatment goal selected for the most troublesome tumor (identified by the investigator) in patients with recurrent or refractory squamous cell carcinoma of the head and neck following up to 6 weekly intratumoral treatments of CEG compared to placebo gel

3. To compare the effect of MPI 5010 to placebo gel on total local tumor volume per patient

4. To evaluate the time to response and TTP for the MTT after local treatment with CEG as compared to placebo gel

5. To assess improvement or stabilization in QOL as measured by FACT-H&N

6. To compare the histopathology of injected lesions that respond to local treatment as outlined above (biopsy optional)

7. To determine plasma platinum levels in patients receiving CEG

1.3.3 Rationale

Head and neck is a common malignancy accounting for 5% of all adult cancer worldwide. Optimal management of advanced head and neck cancer requires multi-modality therapy including surgery, radiotherapy and chemotherapy. The role of chemotherapy remains ill-defined, although local control of disease is enhanced with the use of chemotherapy in conjunction with surgery and radiation therapy. Numerous antineoplastic agents have been studied both alone and in combination in head and neck cancer including cisplatin, methotrexate, bleomycin and 5-fluorouracil. Directed local therapy has been attempted in a variety of different disease settings in an attempt to improve local control and is believed to offer improvements in the therapeutic index. The sponsor has developed a novel formulation of collagen, cisplatin, and epinephrine in the form of a gel that may be used to directly inject head and neck cancer lesions. This gel, known also as MPI 5010, cisplatin-epinephrine gel, cis/epi gel and CEG, has been investigated in a phase 1 dose-escalation setting and has been shown to be safe.

1.3.4 Eligibility Criteria

1.3.4.1 Inclusion Criteria

- Male or female patients at least 18 y/o with histologically-confirmed and documented recurrent or refractory squamous cell carcinoma of the head and neck. Tumors may be primary or metastatic. Involved nodes must be palpable with biopsy-proven cancer. It is preferable for the MTT to have been biopsied prior to study.

  Reviewer comment: There are several issues related to the histological evaluation of a prospective tumor. When is histological confirmation required, at study entry or at sometime during the course of their disease? For the initial diagnosis, will the initial diagnosis be sufficient if established by FNA or is there value to reviewing the surgical specimen? Will the histology at the time of enrollment into the trial be different than that noted at the time of initial diagnosis especially after radiotherapy and chemotherapy?

  Reviewer comment: Is the natural history of the lesion in question dependent on it being a primary lesion versus one of several metastatic lesions? Is the natural history dependent on whether it is a tumor nodule versus an involved lymph node? Is the natural history for a tumor nodule different if it arose *de novo* in a field previously exposed to irradiation or in tissue exposed to prior chemotherapeutic agents rather than unexposed tissue?

- The patient must not require more than 10 mL of CEG. The patient need not have all tumors, present at baseline, selected for treatment. The MTT must be at least 0.5cm3 in volume.

- The patient has been previously treated for head and neck cancer with at least one course of therapy (chemotherapy, surgery, radiotherapy, biological response modifier therapy).

  Reviewer comment: It appears that patients could actually receive nothing except surgery prior to receiving CEG. This does not follow standard of care. Standard of care usually is comprised of surgery +/- radiotherapy followed by chemotherapy for relapses. The review needs to carefully evaluate what the prior therapies were and how the response and/or benefit rate varies with each degree of prior therapy.

- The treatment site(s) are readily measurable and accessible for direct intratumoral injection and in the Investigator's opinion does not pose an immediate risk of hemorrhage or embolization.

  Reviewer comment: What was the preferred method of measurement? Simply a ruler applied to the lesion at right angles or was a caliper employed? How

reproducible was the measurement method? Scanned images would be more verifiable by a reviewer in future studies.

Reviewer comment: By what criteria did the Investigator judge that a MTT does or does not pose a risk of hemorrhage or embolization. Do we know how often this was cited as a reason for not enrolling a screened patient? Are there examples where the investigator judged such to not be a problem and it actually turned out to be one?

- There are two types of treatment goals: those selected by the Investigator (palliative or preventative) and those selected by the patient (palliative).

- The patient must be able to return to the study site for treatment and follow-up visits as defined in the protocol.

- The patient must not have any medical or psychiatric condition that may compromise the ability to give written informed consent.

- The patient must have acceptable screening laboratory evaluations as determined by the investigator in consideration of the patient's general medical health.

- Minimal acceptable hematological parameters:

  ANC > 1000/mm3

  Reviewer comment: the ANC is reasonable but not particularly important from a CEG administration perspective. The systemic exposure is very small and is unlikely to affect marrow function.

  Platelets > 75,000/mm3

  Reviewer comment: the platelet count is reasonable for an invasive procedure with a needle, although a minimum platelet count should be considered.

- Creatinine must be <1.5x above the IULN for the patient's gender

  Reviewer comment: It is not immediately obvious why this should be an eligibility criterion. Even in the presence of a significant diminution in renal function the dose of CDDP contained in the commonly used volumes of CEG drug would not be anticipated to be associated with renal, neurologic or hematologic toxicity. Exceptions would occur under extreme use.

- KPS 60 –100%
- Anticipated survival of at least 6 months
- Patient is fully recovered from any side effect of a previous treatment

1.3.5.2 Exclusion Criteria

- An individual tumor > 20 cm3 will not receive treatment with CEG.

- Systemic disease in tissues such as the liver, lung or pancreas will not receive treatment with CEG

  Reviewer comment: It is not immediately apparent how these exclusions will translate in to potential labeling. Moreover, how carefully were patients evaluated for systemic disease? What spectrum and severity of systemic disease does the sponsor have in mind?

- Fibrotic lesions are excluded (they are defined as a previously irradiated lesion that has not clearly evidence disease progression)

  Reviewer comment: Are these lesions readily recognizable to physicians who would manage these patients? If so, then they should indeed not be treated with CEG. If they are not immediately recognizable, then how will a physician determine *a priori* such a lesion is appropriate?

- Uncontrolled local infection at the treatment site

- Head and neck cancer histology other than squamous cell carcinoma.

- NYHA Class III or greater cardiovascular symptoms or a history of cardiac arrhythmias, where the study treatment, in the opinion of the Investigator, may increase the risk of arrhythmia for the patient.

  Reviewer comment: How will this exclusion appear in the label? NYHA class III patients are quite debilitated. What are the specific criteria describing these patients and what is the correlation between KPS and NYHA class? What were the arrhythmias that were excluded? Will this be a problem in the labeling?

- "The patient must be fully informed of the potential hazard to the fetus if the patient or his partner becomes pregnancy while receiving chemotherapy."

- Known hypersensitivity to cisplatin, bovine collagen, epinephrine or sulfites.

  Reviewer comment: What is the anticipated rate of any one of these in the general population? I believe it to be very low. A reasonable question might be to the reviewers covering collagen about the hypersensitivity risk.

- Pregnant or lactating and breastfeeding females.

  Reviewer comment: Pregnancy and lactation/breastfeeding should be an absolute contraindication for CEG.

- Known history of clinically significant extracranial carotid vascular disease from either atherosclerosis or radiation therapy or previous carotid artery surgery.

- Tumors that directly involve or threaten to invade the carotid artery. These vessels include any tumor in close proximity to a major vessel of the extracranial vascular system such as the common, internal and/or external carotid and/or the vertebral arteries.

  Reviewer comment: This appears to be based on historical data. Perhaps a carotid duplex should be considered when disease may be in the area of the carotid artery. If a careful history is not taken, patients may be at increased and unacceptable risk. Certainly auscultation for carotid bruits should be mandatory as well as an examination for peripheral vascular disease.

1.3.6 Formulation

One mL of active CEG contains the following (v. 21, p. 17-18):

Cisplatin	4 mg
Epinephrine	0.1 mg
Purified bovine collagen	20 mg
Sodium phosphates	
Sodium chloride	
Mannitol	
Sodium metabisulfite	
Polysorbate 80	
Edetate disodium	
Acetic acid	
WFI	
HCl/NaOH to adjust for pH	

Reviewer comment: This list represents a large number of components in this formulation. Are all of these necessary, and what will the stability data support in terms of the individual components and the combined product?

One mL of placebo gel contains the following (v. 21, p. 18):

Sodium chloride	0.9%
Bovine collagen	20mg

There was a difference in color between the two preparations which was minimized by the placement of a mask in order to maintain the blind.

Reviewer comment: Are there ways of testing, *post hoc*, for the validity and/or integrity of the blind?

1.3.7 Experimental Controls

This study compared the active CEG to a placebo gel in a blinded phase lasting 6-8 weeks. This was followed a 4-week evaluation period.

Reviewer comment: It is not clear that during the evaluation phase if the blind was broken. If it was, then responses or toxicity estimates may be biased. This needs to be carefully considered during this review.

1.3.8 Treatment Plan

There were three phases in which each patient passed in this study. The Treatment Phase lasted 2 ½ - 3 months, the Follow-Up Phase lasted 5 months and the Extended Follow-up Phase was of an unspecified duration.

<table>
<tr><th colspan="2">Treatment Phase</th><th>Follow-up Phase</th><th>Extended Follow-up Phase</th></tr>
<tr><td colspan="2">10-12 weeks</td><td>5 months</td><td>Not specified</td></tr>
<tr><td>Treatment Period</td><td>Eval. Period</td><td></td><td></td></tr>
<tr><td>6-8 weeks</td><td>4 weeks</td><td></td><td></td></tr>
</table>

The Treatment Phase was comprised of two portions: a Treatment Period of 6-8 weeks duration and an Evaluation Period lasting 4 weeks.

During the Treatment Period six injections of CEG or placebo gel were administered over 6-8 weeks.

> **Reviewer comment:** The underlying rationale permitting patients receive therapy with 1-2 week gaps during the Treatment Period is not immediately obvious. Alternatively, why was it considered undesirable to plan 6 weekly injections over 6 weeks?

During the Evaluation Period each patient was evaluated weekly for four weeks. No therapy was permitted during this period.

At treatment visit 4 during the Treatment Period the investigator assessed the status of the MTT. Patients with a ≥ 25% increase from baseline (established just prior to the first treatment) were crossed-over to open-label CEG and entered into the Extended Follow-up Phase.

> **Reviewer comment:** What would the outcome be if a patient is randomized to active CEG and then experiences tumor progression while on CEG at 4 weeks? The patient could be crossed-over to placebo.

The dose administered was 0.25 mL gel per cm3 of tumor. The assigned dose was recalculated at each visit based on the size of the tumor at that time.

> **Reviewer comment:** It is possible that the local toxicity, which was evaluated by several different criteria, might be different between the two arms such that the blind was not maintained. It is difficult to anticipate what the impact of this potential unblinding will be on the data derived from these studies.

If new tumors developed during the Treatment Phase, they could be treated with the study drug. Additionally, other tumors, which may have existed at the time of initial treatment, could be

treated with "extra" gel. The important feature was that the total volume of agent administered was ≤ 10 mL.

> **Reviewer comment:** This provision could cause an increased level of local toxicity if the lesions were in the same area. Additionally, the sponsor did not collect safety and efficacy data on these "other" tumors. One might expect a disparity between different lesions with regard to efficacy and toxicity. The rationale underlying this provision is unclear to the medical reviewer.

At each visit during the entire study, patients were requested to complete the Treatment Goal Questionnaire (TGQ).

The FACT H&N QOL Assessment was administered during the screening period, the week 1 Evaluation visit, the week 4 Evaluation visit, the last Follow-up visit, and the last visit on study.

> **Reviewer comment:** The compliance with these evaluations will be important to carefully consider.

1.3.8.1.1 Treatment Interruption

Dosing could be interrupted for severe or intolerable reaction. Each patient whose therapy is interrupted was to return each week until resolution. Treatment may be restarted based on clinical judgement. All such occurrences should be recorded in AE CRF.

> **Reviewer comment:** This parameter will be important to evaluate. No toxicity grades are given which would necessitate treatment interruption, nor are any toxicity grades given as criteria by which to resume therapy.

1.3.8.1.2 Follow-up Phase

If patients experience a CR during the Follow-up Phase, no further therapy will be administered. Patients will be followed monthly for an additional 5 months.

At the end of the Follow-up Phase, patients maintaining a CR for "treated tumors" will continue into the Extended Follow-up Phase.

> **Reviewer comment:** It is not immediately obvious what intervention patients who have *not* achieved a CR will receive. Do they continue to receive active CEG, and if so, on what basis? Clinical judgement? What about the other non-MTT treated tumors? How will a CR in one of the lesions, but not in the MTT, be accounted for in the efficacy analysis?

1.3.8.1.3 Extended Follow-up Phase

In this phase, patients may continue monthly observation if they have a CR or "measurable" response.

Patients may be retreated with CEG.

The first treatment in this phase was at 0.25 mL/cm3. Following this first treatment, the dose may be increased to 0.5 mL/cm3 if the target tumor(s) progress or remain stable with no tissue reaction although the limit of 10 mL of CEG will remain in effect.

Any number of additional tumors may be treated providing the limit of 10 mL is not exceeded.

The "treatment phase" in extended follow-up will be up to 6 treatments in 8 weeks, followed by weekly evaluation for 4 weeks. This "treatment phase" in the extended follow-up phase will be repeated at the discretion of the investigator.

Patients may also receive additional or alternative cancer therapy for tumors which are exhibiting < 100% reduction in tumor volume during this Extended Follow-up Phase. However, such therapy should *not* be administered concomitantly with CEG.

> **Reviewer comment:** Additional agents used in the palliation of tumors while a patient is still on study confound any attempt to achieve a robust understanding of the study agent's efficacy and toxicity.

1.3.8.1.4 Withdrawal Criteria

Patients are withdrawn from this study for the following reasons:

- Disease progression – unless further treatment is judged by the investigator to be safe and potentially beneficial.
- Unacceptable adverse medical experience, including local toxicity

  > **Reviewer comment:** The "unacceptable AE's" should be clearly stated. Why would a patient be dropped from the study for an "unacceptable AE" yet remain on study to receive additional therapy in the face of progressive disease while receiving concomitant non-protocol therapy?

- Delay in scheduled dosing for greater than two weeks, except when a result of resolution of adverse experience
- Need for any treatment not allowed by protocol

  > **Reviewer comment:** This seems to contradict the earlier statement that other anti-cancer therapies could be employed while the patient remains on study.

- Patient decision to discontinue for any reason

> **Reviewer comment:** It is interesting to note that protocol *non-compliance* was not one of the reasons a patient would be withdrawn.

1.3.8.1.5 Biopsy

Patients who achieve a CCR may agree in conjunction with the investigator to undergo biopsy. Representative samples from each quadrant of the treated sites(s) will be obtained.

> **Reviewer comment:** The underlying rationale behind this statement is not immediately obvious. Claims will be based on clinical, not pathological, response. It appears possible that multiple sites may be biopsied, suggesting a tremendous degree of potential bias.

1.3.8.2 Study Visit Requirements

Please refer to the Study Calendar found in Appendix __.

1.3.8.3 Injection Technique

The initial technique by which the study material was injected was a single cutaneous puncture with administration of the total volume at the end of the needle. The underlying assumption was that the gel would creep and ooze its way into the tissue interstitium and remain lodged.

Reflux of the injected material was noted in several patients whose injected tumor. Consequently, that tumor did not receive the protocol-specified dose of the study agent.

The sponsor, at amendment 5, changed the method by which the dose was administered. Following this amendment, the investigators were requested to inject the study agent by "fanning" or by using a grid approach. In each case, the needle was redirected multiple times per administration throughout the volume of the tumor, and small portions of the total dose for that tumor were injected.

1.3.8.4 Efficacy Considerations

1.3.8.4.1 Objective Response Definitions and Criteria

This study used standard terminology employed in oncology drug development:

Clinical Complete Response (CCR): total disappearance of all clinically detectable and evaluable malignant disease, maintained for at least four weeks.

Reviewer comment: The definition of "evaluable" is somewhat unclear and will not be used in the FDA analysis. FDA will evaluate all patients on an ITT basis.

Pathologic Complete Response (PCR): pathologic proof of clinically complete response after biopsy of treated areas of known malignant disease (optional).

Reviewer comment: The definition of "evaluable" is somewhat unclear and will not be used in the FDA analysis. FDA will evaluate all patients on an ITT basis. Additionally, the nature of the CR is not of critical importance to the Agency's analysis. Pathologic CR was not required, per FDA's meeting minutes, prior to commencing enrollment.

Partial Response (PR): Fifty percent or greater reduction in detectable and evaluable malignant disease, maintained for at least 4 weeks.

Stable Disease (SD): < 50% reduction or < 25% increase in detectable and evaluable malignant disease.

Progressive Disease (PD): ≥ 25% increase in detectable and evaluable malignant disease

Time to Onset of Response: the time between initiation of therapy and the onset of PR or CR.

Duration of Response: the time from onset of PR until objective evidence of progression is obtained.

Tumor Length: the greatest diameter

Tumor Width: the greatest perpendicular diameter

Tumor Height: "height and/or depth" of tumor

Note: Areas of necrotic or disease-free tissue and areas with cutaneous reactions such as erythema and swelling should not be included in the target tumor volume.

Tumor Volume = Length x Width x Height x 0.5

Tumor Complete Response (TCR): Reduction in baseline volume of an individual tumor by 100%, sustained for at least 4 weeks (28 days). A TCR may occur at any time after the first treatment whether during the Treatment Phase, Follow-up Phase or Extended Follow-up phase with or without retreatment.

Tumor Partial Response (TPR): Reduction in baseline tumor volume of and individual tumor by 50-99%, sustained for at least 4 weeks (28 days). A PCR may occur at any time after the first treatment whether during the Treatment Phase, Follow-up Phase or Extended Follow-up phase with or without retreatment. *A TPR in which the tumor continues to decrease in size and eventually disappears will be reclassified as a TCR with the same start date as the TPR, provided it meets the criterion of 28 days' duration immediately following the first evidence of 50-99% reduction.*

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TCR's and TPR's will not be affected by the incidence of other tumors.

Tumor Non-Response: Any tumor not meeting the requirements for a TCR or a TPR.

Reviewer comment: There appears to be no accommodation for stable disease.

Patient Complete Response: Reduction of 100% in total volume of all evaluable target tumor(s), sustained for at least 4 weeks (28 days). A PCR could have occurred at any time after the first treatment whether during the Treatment Phase, Follow-up Phase or Extended Follow-up phase with or without retreatment.

If one or more new tumors developed OUTSIDE the treated area (as determined by the investigator) the new tumors may be treated at a dose based on their individual volume and response will NOT affect the classification of the patient as a PCR, which will be based only on the baseline total tumor volume and volumetric change from baseline of original tumors.

If one or more new tumors develop INSIDE the treated area (as determined by the investigator) the patient will be classified as a PCR only if the new tumors also decrease in volume by 100%, and the period of sustained response is 28 days or more for all tumors concurrently. In such a case, the first day of PCR will be the first day on which 100% reduction of all treated tumors, original and incident, is recorded.

Patient Partial Response: Reduction of 50-99% in total volume of all evaluable target tumor(s), sustained for at least 4 weeks (28 days). A PPR could have occurred at any time after the first treatment whether during the Treatment Phase, Follow-up Phase or Extended Follow-up phase with or without retreatment. *A PPR in which all tumors at baseline continue to decrease in size and eventually disappear will be reclassified as a PCR with the same start date as the PPR, provided it meets the criterion of 28 days' duration immediately following the first evidence of 50-99% reduction.*

If one or more new tumors developed *outside* the treated area (as determined by the investigator) the new tumors may be treated at a dose based on their individual volume and response will *not* affect the classification of the patient as a PCR, which will be based only on the baseline total tumor volume and volumetric change from baseline of original tumors.

If one or more new tumors develop *inside* the treated areas (as determined by the investigator) the patient will be classified as a PPR

only if the new tumors also decrease in volume by 50-100% (a PPR or PCR) and the period of sustained response is 28 days or more for all tumors concurrently**.**

Progressive disease (presumably for both per-tumor and per-patient determinations):

If progression criteria are met for at least one target tumor or if new tumors appear within the treated area. Additionally, patients who experience a deterioration in KPS > 10% related to malignant disease at the target site(s), not target tumors or other malignant disease will be considered to have progressed.

Reviewer comment: Do these criteria make reasonable sense? Thus far in the protocol, "target lesions" have not been defined. What defines a lesion as a "target" lesion and where is it found? Moreover, how certain can the study investigators be about the what a drop in KPS is due to? Progressive disease, a decline in the hemoglobin level or a general medical decline could be responsible. This criterion does not appear to be standardized across study sites.

Note: stabilization or progression of disease other than at the target site(s) or outside the treated area will not detract from a patient PR or CR of the target sites(s).

1.3.8.4.2 Efficacy Analysis

A more detailed discussion about the statistical issues may be found in the statistical review.

The primary efficacy for this study is based on tumor response of the MTT excluding the third stratum. All other analyses will be performed using all strata. All analyses will take into account the change in the dose assignment described in Amendment 5.

Reviewer comment: This primary efficacy analysis endpoint is different than what the meeting minutes indicates the Agency communicated to the applicant. In the review of the regulatory history of this NDA it is apparent that emphasis was placed on evidence of clinical benefit with the objective responses playing a supportive role. In addition, both of these endpoints must be highly correlated.

Baseline demographic, historical and tumor specific data described by the following parameters will be analyzed by summary statistics.

Baseline Parameters

Age
Sex
Race
MTT Volume
Total Tumor Volume
Number of Tumors
Medical History
Treatment History

Progress towards the selected Treatment Goals will be evaluated by Goal category across treatment groups. ANOVA or ANCOVA will be used to evaluate the variance of treatment goal scores using tumor volume as a covariate.

The reliability of the Palliative Treatment Goal questionnaire will be investigated using McNemar's test. An attempt to validate the questionnaire will be made.

The results from the Preventative Treatment Goal questionnaire will be analyzed by the Mantel-Haenzel chi-squared test. An attempt to validate the Preventative Treatment Goal questionnaire will be made.

The extent of agreement between patient and physician will be evaluated in the subsample of patients in which the patient and physician selected the same goal. This will be analyzed using the kappa statistic.

Quality of Life as determined by the FACT H&N instrument will be evaluated by nonparametric analysis of variance and test for trend. The association of subscale and overall responses with KPS will be examined using Spearman's correlation coefficient.

Tumor response data will be evaluated using ANOVA or ANCOVA and Mantel-Haenzel chi-squared statistic.

Time to MTT CR will be compared across treatment groups using Kaplan-Meier methods with baseline total tumor volume as a covariate.

Time to recurrence (also termed the duration of response) will be compared between treatment groups using the Kaplan-Meier method.

Time to disease progression will be compared across treatment groups using the Kaplan-Meier method.

Patient responses of patients initially treated with placebo and then treated with open-label CEG will be contrasted using a paired design.

"Analytic methods" used for the MTT will be used to evaluate total patient response. Responses in individual treated tumors other than the MTT will be assessed descriptively.

The number and percent of tumors with complete response, partial response, stable disease and progressive disease at the end of the Treatment Phase will be tabulated by treatment group.

1.3.8.4.3 Pharmacokinetic Analysis

Serum samples were obtained at visits 1 and 3 (during the blinded Treatment Phase) and the investigators, clinical research staff and sponsor remained blind to the results. The parameters Cmax, Tmax, and the absorption and elimination half-lives were determined. The AUC (0→t) was determined by the trapezoidal method and AUC (0→infinity) was estimated for each patient.

A single sample for serum platinum levels was obtained prior to dosing at visit 2.

Reviewer comment: This description seems rather brief.

1.3.8.4.4 Safety Considerations

Adverse events were classified by the following criteria:

Category (immediate injection effect, local reaction, systemic reaction)
Body system
Preferred term
Severity
Relationship to study drug

Serious AE's were described textually.

Tumor conditions at the treatment site(s) were assessed at each visit and graded on a four-point scale (absent, mild, moderate, severe). The proportion of patients in each treatment group experiencing tumor symptoms was tabulated by visit.

Reviewer comment: The protocol specifies the use of the NCCOG/NCI Criteria (1991).

Appendix D

Regulatory History of IND 38,356, NDA 21-236, Cisplatin/Epinephrine Gel

Emphasizing the most relevant clinical and statistical agreements between the division and the sponsor.

12/19/94 Meeting	Discussed sponsor's development plan Two studies proposed for head and neck cancer: US and Europe Specific emphasis was on <u>treatment goals</u> Must be acceptable to the FDA Should be chosen not only by patient <u>Target goal of extreme importance</u> Local toxicities important to capture Control arm would be collagen + epinephrine Blinding would be helpful Concern over blinding expressed because of yellow color of active drug Statistical concerns: Handling missing values Prognostic factors, which should be specified Co-variates, which should be specified
12/3/97 Meeting	Full study reports will be submitted All photographs will be submitted Sponsor will specify primary endpoint and analyses A uniform method for determining and analyzing a patient benefit for **<u>each</u>** patient should be proposed ASAP The primary analysis will be symptom improvement; tumor responses are expected to be supportive. Adjustments will be unnecessary "Symptomatic response" strongly recommended as primary efficacy endpoint The association of TG attainment and MTT response will be analyzed
10/28/99 Meeting	Clinical benefit and response analyses should be based on the ITT population. All other analyses will be considered exploratory Perform subset analysis for patients who are considered incurable with surgery Extensively describe the previous therapies to document refractoriness of the Disease
5/8/00 Response to 10/28/99 Meeting	The Agency will require a strong correlation between tumor shrinkage and patient benefit in individual responders. FDA will not require adjustment of the nominal Type 1 error. FDA recommends that the sponsor analyze the patient benefit questionnaire and the response rate as co-primary endpoints using a type 1 error level of 0.05 for each analysis. The correlation between the patient benefit and response rate needs to be large The FDA reviewer must agree with the adequacy of the prospectively defined treatment goal Patient benefit is described as an improvement of one scale point or more from baseline in the treatment goal. Depending on the scale used, improvement of only one point may not be sufficient to determine patient benefit. Clinical benefit without adequate duration of response is not meaningful Clinical benefit during the extended follow-up phase for patients who received

additional therapies after treatment [with CEG] will be viewed with skepticism. These additional therapies may have a confounding effect on the efficacy analysis.

Appendix E

Reproduction of the Palliative and Preventative Treatment Goal Scale

General Instructions

At the screening visit, each patient is to select one or more treatment goals from one of the eight palliative treatment goal categories: wound care, pain control, ability to see, ability to hear, ability to smell, physical appearance, obstructive symptoms, or mobility. The treatment goals should reflect the patient's desire to improve his/her physical or social functioning in a personally meaningful way as a direct result of treatment with cisplatin/epi gel.

Because the scales are designed to measure improvement, the patient should not select treatment goal categories in which he/she would place himself at the best end of the four-point measurement scale.

One to eight palliative treatment goals may be selected by the patient; the goals will be assessed at screening and the beginning of every treatment and follow up visit.

Some patients may be unable to identify any treatment goals. This would occur, for example, if the patient's self-assessment placed him at the best end of the scale in every goal category. A patient who is unable to select a treatment goal category will have the change in tumor volume of his/her treated tumors used in place of the treatment goal. The overall tumor response will also be measured on a four-point scale: complete response (100% reduction in tumor volume), partial response (50% or greater reduction in tumor volume), stable disease (less than 50% reduction or increase of less than 25% in tumor volume) and disease progression (25% or greater increase in tumor volume).

At the time the patient selects treatment goals, the physician should also select one or more treatment goals for that patient. A primary treatment goal must be identified by the physician for the patient's most troublesome goal. The patient and physician need not discuss their reasons for selecting treatment goals, and the patient and physician need not select the same goals.

The patient may select one or more treatment goals from eight palliative goals: wound care, pain control, ability to see, ability to hear, ability to smell, physical appearance, obstructive symptoms, or mobility (unless he/she is unable to select a treatment goal, as described above).The physician may select goals from the list of eight palliative goals and the list of three preventive goals: invasion, obstruction, and subcutaneous tumors breaking through the skin.

At each visit, the patient will assess his/her current status on the palliative treatment goals he/she selected at the first visit, rating his/her status on each goal on a four-point scale.

If the physician selected palliative goals for the patient, he/she will also rate the patient's status on each goal at each patient visit. Status on preventive goals will be rated by the physician on a two-point scale (prevented or failed to prevent). Preventive goals will be evaluated and rated only at screening, week 4 evaluation visit, end of follow-up (month 5), and study completion.

For patients who terminate the initial treatment stage after less than six treatments and who do not have a CR, preventive goal assessment should be done before administration of open-label drug.

1. Prevention Scales: Physician Assessment Only

    1. Prevention of invasion of vital structure(s) and/or blood vessel(s).
    Specify structures and/or vessels threatened by invasion:
    _____
    _____

    I . At end of 4-week follow-up, tumor has not invaded vital organs or blood vessels. If patient terminates initial treatment prematurely, evaluate at last visit of initial treatment phase before administration of open-label drug.

    2. At end of 4-week follow-up, tumor has invaded vital organs and/or blood vessels. If patient terminates initial treatment prematurely, evaluate at last -visit before administration of open-label drug.

        Date of invasion:_____

2. Prevention of obstruction

    Specify structures, areas, and/or processes threatened by obstruction:
    _____
    _____

    1. At end of 4-week follow-up, tumor has not obstructed any structure, area, or process in a manner which interferes with the patient's functioning. If patient terminates initial treatment prematurely, evaluate at last visit before administration of open-label drug.

    2. At end of 4-week follow-up, tumor has progressed to obstruct a structure, area, or process in a manner which interferes with the patient's functioning. If patient terminates initial treatment prematurely, evaluate at last visit before administration of open-label drug.

        Date of obstruction:_____

3.Prevention of subcutaneous tumors breaking through the skin.

Specify location of at risk of breaking through the skin:
_____
_____

1. At end of 4-week follow-up, a subcutaneous tumor has not broken through the skin to create an ulceration, erosion, or hole. If patient terminates initial treatment prematurely, evaluate at last visit before administration of open-label drug.
2. At end of 4-week follow-up, a subcutaneous tumor has broken through the skin to create an ulceration, erosion, or hole. If patient terminates initial treatment prematurely, evaluate at last visit before administration of open-label drug.

Date tumor broke through skin:_____

II. Palliation Scales: May be Selected by Patient or Physician

I . Wound Care

Instructions to patient:

Please choose the statement below which best describes your cancer sore (or sores) over the past week [SUBSTITUTE: "since your last visit" for subsequent visits].

Please choose a response based only on the sore or sores injected with medicine as part of this study.

If some of your treated sores are worse than others, choose statement which describes the worst treated sore.

1. 1 do not have an open sore that oozes, bleeds, or smells bad.

2. 1 have an open sore that has little or no smell and does not need a bandage.

3 1 have an open sore that needs a bandage and/or has a bad smell, but the smell does not stop me from being around other people, or make me feel sick to my stomach.

4. 1 have an open sore that needs frequent changes of bandage or packing; OR has a strong/bad smell that stops me from being around other people; OR causes me to feel sick to my stomach or to vomit.

2. Pain Control

Instructions to patient:

Please choose the statement below which best describes the pain you have felt over the past week [SUBSTITUTE: "since your last study visit" for subsequent visits].

Please answer based on only on the tumor or tumors injected with medicine as part of this study. Choose the statement that describes the pain caused by your tumor(s).

Do not include pain caused by the injection of medicine into your tumor(s), either at the time of the injection or later.

If some of your treated tumors are causing more pain than others, choose a statement that describes the treated tumor giving you the most pain.

1. 1 have no pain, or I have minor pain that does not require medicine.
2. 1 have pain that goes away when I take medicine that I can buy in the drugstore without a doctor's prescription.
3. 1 have pain that only goes away when I take medicine prescribed by a doctor.
4. 1 have pain that does not go away even when I take medicine prescribed by a doctor.

3. Ability to See

Instructions to patient:

Please choose the statement below which best describes your sight over the past week [SUBSTITUTE: "since your last study visit" for subsequent visits], compared to before your illness.

These statements are about problems you may have with your sight that are caused by one or more of the tumors being treated in this study.

Please choose the statement that most closely describes the problems with your sight caused by the treated tumor(s).

1. 1 can see just as well as I could before my illness.
2. 1 cannot see as well as I could before my illness, but I am able to do things like watch TV and read.
3. 1 cannot see as well as I could before my illness, and this makes it hard for me to read and watch TV.
4. 1 cannot see.

4. Ability to Hear

Instructions to patient:

Please choose the statement below which best describes your hearing over the past week [SUBSTITUTE: "since your last study visit" for subsequent visits], compared to before your illness.

These statements are about problems you may have with your hearing that are caused by one or more of the tumors being treated in this study.

Please choose the statement that most closely describes the problems with your hearing caused by the treated tumor(s).

1. 1 can hear just as well as I could before my illness.
2. 1 cannot hear as well as I could before my illness, but I am able to do things like watch TV, listen to the radio, and talk with people.
3. 1 cannot hear as well as I could before my illness, and this makes it hard for me to watch TV, listen to the radio, and talk with people.
3. 1 cannot hear.

5. Ability to Smell

Instructions to patient:

Please choose the statement below which best describes your sense of smell over the past week [SUBSTITUTE: "since your last study visit" for subsequent visits], compared to before your illness.

These statements are about problems you may have with your sense of smell that are caused by one or more of the tumors being treated in this study.

Please choose the statement that most closely describes the problems with your sense of smell caused by the treated tumor(s).

I . I can smell just as well as I could before my illness.

2. 1 cannot smell as well as I could before my illness, but it does not effect my enjoyment of food or things around me.

3. 1 cannot smell as well as I could before my illness, and I do not enjoy my food or things around me as much as I used to.

4. 1 cannot smell.

6. Physical Appearance

Instructions to patient:

Please choose the statement below which best describes how you have been feeling about the way you look over the last week [SUBSTITUTE: "since your last study visit" for subsequent visits].

Please choose your answer based only on things about the way you look that might be changed by injections with study medicine.

If you think that some things about the way you look are getting worse due to the injections but some are getting better, try to choose a sentence that best describes your overall feeling about the way you look.

1. My illness has not changed the way I look much.

2. 1 have some scars from my illness, but no one can tell that I am ill.

3. People can tell by looking at me that I am ill, but this does not stop me from going out and meeting people.

4.1 don't like to go out in public because of the effect my illness has had on the way I look.

7. Obstructive Symptoms

Instructions to patient:

Please choose the statement below which best describes your symptom or symptoms over the last week [SUBSTITUTE: "since your last study visit" for subsequent visits]. Please choose your answer based on only symptoms you feel are caused by tumors injected with medicine as part of this study.

The answer may be about only one symptom (difficulty swallowing, for example). It may be about more than one (difficulty swallowing and also difficulty breathing, for example).

If you have more than one symptom and one is worse than the other, pick the sentence that describes the worst symptom.

1. My illness does not interfere with my ability to talk, breath, or eat.
2. Because of my illness, I have minor trouble with talking, breathing, or eating. For example, I can't eat everything I like because I have trouble swallowing.
3. Because of my illness, I have a lot of trouble talking, breathing, or eating. For example, I can eat only soft foods or liquids because I have trouble swallowing.
4. Because of my illness, I can't talk, or I need a tube to breath, or I am fed through a tube.

8. Mobility

Instructions to patient

Please choose the statement below which best describes your ability to move around and use all parts of your body (arms, legs, neck, trunk, etc.) over the past week [SUBSTITUTE: "since your last visit" for subsequent visits].

These statements are about problems with movement that are caused by one or more of the tumors being treated in this study.

Please choose the statement that most clearly describes the problem with moving around caused by the treated tumor(s).

1. 1 am able to move around as well as I could before my illness.
2. Because of my illness, I have some problems with moving around, but I can still carry out most of my normal everyday activities.
3. Because of my illness, I have problems with moving around that greatly affect my normal everyday activities. (Examples: I can no longer move around well enough to drive a car; I can no longer move around enough to fix a meal for myself.)
4. Because of my illness, I can no longer move around at all, or I can only move around a very little. There are almost no normal everyday activities I can carry out by myself.

What part of your body do you have problems moving?_____

Appendix F

Treatment Plan

BLINDED PERIOD			OPEN-LABEL PERIOD
Treatment Phase		*Follow-up Phase*	*Extended Follow-up Phase*
6 to 8 weeks	*4 weeks*	*Up to 5 months*	
• Treat MTT and other selected tumors with CDDP/epi or placebo gel* for 6 weekly treatments or until 100% reduction of total treated tumor volume, whichever occurs first. • Assess disease progression. • Complete responders (100% reduction of total tumor volume) may enter Follow-up • Patients with a partial response, stable disease, or disease progression may enter Extended Follow-up to receive open label CDDP/epi gel	• Evaluate response (once each week)	• Follow duration of response (monthly) • Patients who maintained a complete response could enter Extended Follow-up for continued follow-up • Patients with disease progression could enter Extended Follow-up for retreatment	• Follow duration of response (monthly) for responders • Retreat new, progressive, and recurrent tumors with open-label CDDP/epi gel * • Receive treatment with other cancer therapy†

* New tumors that developed during the Treatment Phase could also be treated, provided that the total assigned patient dose did not exceed 10 mL CDDP/epi or placebo gel

† Other cancer therapy was not to be administered concomitantly with CDDP/epi gel unless approved by Matrix.

Appendix G

Randomized Studies of Combination Chemotherapy in Recurrent and Metastatic SCC of the Head and Neck

Regimen	n	Response Rate (%)	Response Duration (mo)	Median Survival (mo)	Author
Platinum + 5-FU (bolus)	20	20	--	5.0	
vs.					Kish, 1985
Platinum + 5-FU (infusion)	18	74	--	6.7	
MTX+Bleo+Vincristine	75	29	4.3	7.3	
vs.					Clavel, 1987
MTX+Bleo+Vincr+Platinum	85	51	6.8	8.5	
MTX + 5-FU (sequential)	14	43	--	--	
Vs.					Browman, 1988
MTX + 5-FU (simultaneous)	18	67	--	--	
Platinum + 5-FU	28	46	--	6.0	
vs.					Amrein, 1992
Platinum+5-FU+MTX+Bleo	27	63	--	6.0	
Platinum + MTX + Bleo	19	31	1.5	--	
vs.					Paccagnella, 1989
Epirubicin + MTX + Bleo	47	47	2.3	--	
Platinum + Taxol (high dose)	105	35	4.1	7.6	
vs.					Forastiere, 2001
Platinum + Taxol (low dose)	104	36	4.0	6.8	
Platinum + 5-FU	122	47	--	6.3	
vs.					Schrijvers, 1998
Platinum + 5-FU + IFN-α_{2b}	122	38	--	6.0	

Source: DeVita, 6th, p. 810

Randomized Studies of Single-Agent vs. Combination Chemotherapy in Recurrent and Metastatic SCC of the Head and Neck

Regimen	n	Response Rate (%)	Response Duration (mo)	Median Survival (mo)	Author
Platinum		13		--	
vs.					Davis, 1979
Platinum + MTX + Bleo		11		--	
Platinum		18		6.9	
vs.					Jacobs, 1983
Platinum + MTX		33		6.2	
MTX		33		6.0	
vs.					Drelichman, 1983
Platinum + Vincristine + Bleo		41		4.3	
Best Supportive Care		--		2.1	
vs.					
Platinum		24		4.2	
vs.					Morton, 1985
Bleo		14		2.8	
vs.					
Platinum + Bleo		13		4.0	
MTX		35		5.6	
vs.					Vogl, 1985
MTX + Platinum + Bleo		48		5.6	
MTX		16		7.0	
vs.					Williams, 1986
Platinum + Vinblastine + Bleo		24		7.0	
MTX		19		6.0	
Platinum		40		6.0	Campbell, 1987
Platinum + MTX		31		6.0	
Platinum + 5-FU		33		6.0	
MTX		25		6.0	
vs.					Eisenberger, 1989
MTX + Carboplatin		25		6.0	
Platinum		14		6.0	
Platinum + 5-FU		12		6.0	Liverpool Study, 1990
MTX		6		2.0	
Platinum + MTX		11		6.0	
Platinum		17		5.0	
5-FU		13		6.1	Jacobs, 1992
Platinum + 5-FU		32		5.5	
MTX		10		5.6	
Platinum + 5-FU		32		6.6	Forastiere, 1992
Carboplatin + 5-FU		21		5.0	
Platinum		15		7.0	
Platinum + 5-FU		31		7.0	Clavel, 1994
Platinum+MTX+Bleo+Vincr		34		7.0	

Source: DeVita, 6th, p. 809

Pooled Results of Single-Agent Chemotherapy Studies in Recurrent and Metastatic SCC of the Head and Neck

Regimen	n	Response Rate (%)
MTX	988	31
Bleo	347	21
Cisplatin (Platinum)	288	28
Carboplatin	169	22
5-FU	118	15
Ifosfamide	120	23
Paclitaxel (mg/m2)		
250 (24 h)	73	40
175 (24 h)	41	20
175 (3 hr)	60	15
Docetaxel (mg/m2)		
100 (1 hr)	89	33
60 (1 hr)	23	30
Vinorelbine	102	18
Gemcitabine	54	13
Topotecan	43	14

Source: DeVita, 6th, p. 806

Single-Arm Studies of Taxane-Based Combination Chemotherapy in Recurrent SCC of the Head and Neck

Regimen	n	Response Rate (%)	Author
Paclitaxel + Cisplatin	23	32	Licitra, 1997
Paclitaxel + Carboplatin	49	33	Fountzilas,1997
Paclitaxel + Cisplatin + 5-FU	23	38	Benasso, 1997
Paclitaxel + Cisplatin + Ifos	52	58	Shin, 1998
Paclitaxel + Carbo + Ifosfamide	38	55	Shin, 1999
Paclitaxel + Gemcitabine	44	41	Fountzilas,1999
Docetaxel + Cisplatin	33	52	Forastiere, 1998
Docetaxel + 5-FU	44	54	Fillippi, 1999
Docetaxel + Vinorelbine	27	44	Airoldi, 1999

Source: DeVita, 6th, p. 808